NCT #	NCT03107611
Study Identification Code	CD-14-875
Protocol Version	2.0
Protocol Issue Date	14 October 2016
Study Title	A Randomized, Prospective, Multicenter, Double Blind, Parallel Assignment, Placebo Controlled Bioequivalence Study of Pimecrolimus Cream, 1% and Elidel® (Pimecrolimus) Cream, 1% in Patients with Mild to Moderate Atopic Dermatitis
Sponsor	DPT Laboratories, Ltd., an affiliate of Mylan Inc.

CLINICAL STUDY PROTOCOL

Study Identification Code	CD-14-875
Protocol Version	2.0
Protocol Issue Date	14 October 2016
Study Title	A Randomized, Prospective, Multicenter, Double Blind, Parallel Assignment, Placebo Controlled Bioequivalence Study of Pimecrolimus Cream, 1% and Elidel® (Pimecrolimus) Cream, 1% in Patients with Mild to Moderate Atopic Dermatitis
Study Design	Randomized, prospective, multicenter, double blind, parallel assignment, placebo-controlled, bioequivalence clinical endpoint study
Study Population	Mild to Moderate Atopic Dermatitis
Study Drug	Pimecrolimus Cream, 1%
Sponsor	DPT Laboratories, Ltd., an affiliate of Mylan Inc. 318 McCullough San Antonio, TX 78215
Contact Research Organization (CRO) & Protocol Author	TKL Research, Inc. 365 W. Passaic Street, Suite 550 Rochelle Park, NJ 07662 Phone: 201-587-0500 Fax: 201-336-1512

SPONSOR / CRO APPROVAL PAGE

I have read and understood Protocol No. CD-14- 875 and it meets requirements for the conduct of the study according to US regulatory requirements and all other pertinent requirements of ICH E6 (R1) Good Clinical Practice (Step 5) guidance on good clinical practice, and the Declaration of Helsinki (Fortaleza, Brazil, October 2013).

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Kathleen Ocasio — October 17, 2016

Signature — Date

I have read and understood Protocol No. CD-14- 875 and it meets requirements for the conduct of the study according to local and US regulatory requirements and all other pertinent requirements of ICH E6 (R1) Good Clinical Practice (Step 5) guidance on good clinical practice, the Declaration of Helsinki (Fortaleza, Brazil, October 2013), procedures oriented to good laboratory practices, and the current rules and regulations in force in the countries in which the study is being conducted.

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Sophie Gorengaut — 14 October 2016

Signature — Date

INVESTIGATOR PROTOCOL AGREEMENT

I have read and understood the Protocol No. CD-14-875. I have fully discussed the objectives and design of this study and the contents of this protocol with the Sponsor's representative or designee.

I agree to maintain a list of appropriately qualified persons to whom I shall delegate certain specified trial-related duties based on their training and experience. I shall ensure that all persons assisting me with the trial are adequately informed about the protocol and any amendments, and their trial-related duties and functions.

I understand that the information in this protocol and all other information provided to or accessed by me relating to this study or its progress are the confidential property of the Sponsor and shall not be disclosed, other than to those authorized persons who are directly involved in the execution or the Institutional Review Board (IRB) and/or Ethics Committee review of the study, without prior written authorization from the Sponsor, and I agree to maintain all such information in strict confidence and to use such information solely pursuant to my conduct of the study. It is, however, permissible to provide information to a subject in order to obtain subject consent to participate in the study once IRB approval is obtained.

I agree to conduct this study according to this protocol and to comply with its requirements, subject ethical and safety considerations and guidelines, and to conduct the trial in accordance with ICH guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements. I further agree to comply with local laws and regulations and the provisions of Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the rules and regulations in force in this country at present.

I understand that the Sponsor may decide to suspend or terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

_____

Signature of Investigator

Printed Name:

Date:

BIOSTATISTICIAN SIGNATURE PAGE

I have read this protocol and I agree to conduct the study as described, in compliance with Good Clinical Practice (ICH E6), the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the rules and regulations.

Carol Udell
Carol Udell (Oct 21, 2016)

Signature of CRO Biostatistician

Carol Udell
Printed Name:

Oct 21, 2016
Date:

STUDY SYNOPSIS

Study Title	A Randomized, Prospective, Multicenter, Double Blind, Parallel Assignment, Placebo Controlled Bioequivalence Study of Pimecrolimus Cream, 1% and Elidel® (Pimecrolimus) Cream, 1% in Patients with Mild to Moderate Atopic Dermatitis
Study Design	Randomized, prospective, multicenter, double blind, parallel assignment, placebo controlled therapeutic equivalence study
Sample Size	648 Subjects
Protocol Number	CD-14-875
Study Center	Multi-center study
Study Type	Bioequivalence study with clinical endpoints
Sponsor	DPT Laboratories, Ltd., an affiliate of Mylan Inc. 318 McCullough San Antonio, TX 78215
Investigational Products & Study Arms	**Test drug:** Pimecrolimus Cream, 1% **Reference listed drug (RLD):** Elidel® (Pimecrolimus) Cream 1% **Placebo:** Vehicle cream
Dosage of Investigational Product	A thin layer is to be applied to all affected skin areas twice daily for 2 weeks (14 days)
Objectives	**Primary Objective:** • To establish the bioequivalence between test and reference listed drugs using the primary endpoint in the Per Protocol population **Additional:** • To establish superiority of the each treatment over the placebo using the primary endpoint in the modified intent to treat (mITT) population and Last Observation Carried Forward (LOCF) • To assess individual signs and symptoms of Atopic Dermatitis (i.e., erythema, induration/papulation, lichenification and pruritus) in each treatment group • To compare the safety and tolerability between the test and reference drugs
Study Population	Non-immunocompromised males and females with mild to moderate atopic dermatitis who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. **Age:** 8 years and above

Patient Selection	**Screening Criteria:** • Non-immunocompromised male or female aged 8 years and older • Clinical diagnosis of mild to moderate atopic dermatitis (AD), as defined by the criteria of Hanifin and Rajka • Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.) • An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3) • Affected area of AD involvement at least 5% body surface area (BSA) • Expected to be able to meet inclusion and exclusion criteria after minimum 7 days of continuous treatment with a bland emollient (e.g. Cetaphil® Lotion) **Inclusion Criteria:** • Non-immunocompromised male or female aged 8 years and older • Clinical diagnosis of mild to moderate atopic dermatitis (AD), as defined by the criteria of Hanifin and Rajka • Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.) • A diagnosis of AD for at least 3 months (Subject/guardian may verbally report signs and symptoms of atopic dermatitis with an onset at least 3 months prior.) • An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3) • Affected area of AD involvement at least 5% body surface area (BSA) • Treated with a bland emollient (e.g. Cetaphil® Lotion) for at least 7 days continuously • Willing and able to give written informed consent (and assent as applicable) and willing to comply with the trial protocol • If female of childbearing age, willing to use an acceptable form of birth control, that is stable at least 3 months prior to baseline and throughout the study. Acceptable forms of birth control include any of the following: (1) hormonal birth control, which must be stable for > 3 months prior to baseline; (2) abstinence; subject must use condom plus spermicide, if becomes sexually active; (3) double barrier method, such as condom plus spermicide.

	Exclusion 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, impetigo) 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, ichthyosis, or scabies 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) Concurrent disease or treatment likely to interfere with the study treatment or evaluations g) Use within one month prior to baseline ➢ Oral or intravenous corticosteroids (Subjects on a stable and continued dose of nasal, or inhaled corticosteroids for conditions other than atopic dermatitis may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study. Ophthalmic corticosteroids are not excluded.) ➢ UVA/UVB therapy ➢ PUVA (psoralen plus ultraviolet A) therapy ➢ Tanning booths ➢ Nonprescription UV light sources ➢ Immunomodulators or immunosuppressive therapies ➢ Interferon ➢ Cytotoxic drugs ➢ Tacrolimus ➢ Pimecrolimus h) Use within 14 days of baseline of ➢ Systemic antibiotics ➢ Calcipotriene or other vitamin D preparations ➢ Retinoids i) Use within 7 days prior to baseline of ➢ Systemic antihistamines (Subjects on a stable and continued dose of systemic antihistamines may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study.) ➢ Topical antibiotics

	➢ Topical corticosteroids ➢ Other topical drug products ➢ Probiotics j) 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 (e.g. Cetaphil® Lotion) k) Known allergy or hypersensitivity to pimecrolimus or any other component of the test product or RLD l) Not willing to minimize or avoid natural and artificial sunlight exposure during treatment m) Currently enrolled in an investigational drug or device study or used an investigational drug or investigational device treatment within 30 days prior to first application of the test article
Study Treatment	• **Screening period:** Up to 14 days before visit 2 • **Treatment period:** The blinded treatment will be administered for two weeks for each subject. Apply a thin layer of cream to all affected skin areas twice daily.
Randomization	1:1:1 (Test: RLD: Placebo)
Study Duration	The study duration for each subject would be up to 32 days. There is a screening period of up to 14 days and a treatment period of 14 (± 3) days.
Study Visits	**4 Visits:** V1-Screening Visit (up to -14 days) V2-Baseline and Randomization Visit (Day 1) V3-Interim Visit (Day 8 ± 3 days) V4- End of Therapy Visit (Day 15 ± 3 days)
Study Measurements	**Efficacy:** Signs and Symptoms of Atopic Dermatitis will be scored per body region (Head and Neck; Trunk; Upper Limbs; Lower Limbs). Signs and Symptoms will be scored by the principal investigator or a qualified person delegated by the investigator. It is strongly preferred to have one evaluator for each of the visits per subject. A back up evaluator may be present at baseline in case the primary evaluator is unavailable at follow up. Pruritus will be assessed by questioning the subject or the subject's guardian regarding the intensity in the 24 hours prior to the visit for the overall condition.

Sign and Symptom	Score	Category	Definition
Erythema	0	None	No erythema present
	1	Mild	Slight erythema: very light-pink
	2	Moderate	Dull red, clearly distinguishable
	3	Severe	Deep/dark red
Induration/ Papulation	0	None	None
	1	Mild	Slightly perceptible elevation
	2	Moderate	Clearly perceptible elevation but not extensive
	3	Severe	Marked and extensive elevation
Lichenification	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
Pruritus	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

Overall Body Surface Area (BSA) Involvement with AD will be assessed and recorded by the investigator or delegate.

Investigator's Global Assessment of Disease Severity Scoring will be scored for the investigator's (or delegate's) assessment of the subject's overall condition as seen at the time of evaluation (static) as explained below:

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

Safety:
Physical Examination: Must include a detailed skin examination. Additionally, examination of head, ears, nose and throat, eyes, central nervous system, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system should be assessed.
Vital Signs: Pulse rate, blood pressure and body temperature
Urine Pregnancy Test
Adverse Event Assessments
Application site reactions such as dryness, burning/stinging, erosion, edema, and pain will be assessed scored (as per Appendix IV) and recorded.

Study Endpoints

Primary endpoint:
- The proportion of subjects in each treatment group with treatment success (i.e., 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 at the end of treatment (Study Day 15)

Additional endpoints:
- 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) are considered supportive information
- Application site reactions will be compared between treatment groups.

Safety Endpoints:
Safety assessment through the incidences and severity of all adverse events (AEs) reported during the study and summarized by treatment group

Statistical Analysis:

- Therapeutic equivalence of the test product to the reference product will be evaluated in the PP population. To establish bioequivalence, if the 90% confidence interval (calculated using Yates' continuity correction) of the test - reference difference between products for the primary endpoint (success proportion) is contained within [-0.20, +0.20], then bioequivalence of the test product to the reference

	product will be considered to have been demonstrated. • As a parameter for determining adequate study sensitivity, the test product and RLD will be compared to placebo with regard to the primary endpoint from baseline to week 2 (Day 15). Superiority of the test and reference products against the placebo will be tested at the 5% significance level ($p < 0.05$; using Fisher's exact test) in the mITT population using last observation carried forward. • Supportive information will be presented describing the 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). • Adverse events that occurred subsequent to the first dose of study drug will be summarized. The number and the proportion of subjects who experienced AEs will be computed by treatment group. AEs will also be summarized by each severity grade (mild, moderate, severe) and by each relationship grade (none, possibly, probably) in a similar way. • Application site reactions will be compared via a descriptive analysis between treatment groups.

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ABBREVIATIONS:

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
BSA	Body Surface Area
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGA	Investigator Global Assessment
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
mITT	Modified Intention To Treat
OGD	Office of Generic Drugs
PI	Principal Investigator
PIS	Patient Information System
PP	Per Protocol
SD	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analyzing System
SOP	Standard Operating Procedure
TMF	Trial Master File

1 INTRODUCTION

STUDY DISEASE:

Atopic dermatitis (AD) (eczema) is a skin disease affecting an estimated 35 million Americans, predominantly children.[13] AD is a pruritic disease of unknown origin that starts in early infancy; an adult-onset variant is recognized[14]; it is characterized by pruritus, eczematous lesions, xerosis (dry skin) and lichenification. AD may be associated with other atopic (immunoglobulin E [Ig E]–associated) diseases (e. g., acute allergic reaction to foods, asthma, urticaria, and allergic rhinitis). AD is the first disease to present in a series of allergic diseases such as food allergy, asthma, and allergic rhinitis, provoking the "atopic march" theory, which suggests that early or severe AD and cutaneous sensitization to environmental allergens may lead to subsequent allergic disease at other epithelial barrier surfaces (e.g., gastrointestinal or respiratory tract).[14] This hypothesis is supported by cross-sectional and longitudinal studies.

TREATMENT OPTIONS[15]

Topical steroids in atopic dermatitis

- Topical steroids are currently the mainstay of treatment in association with moisturization.

Immunomodulators in atopic dermatitis

- Tacrolimus (topical FK506) is an immune modulator that acts as a calcineurin inhibitor. In the US, Tacrolimus is available as an ointment and is indicated as a second-line therapy for the short-term and non-continuous chronic treatment of moderate-to-severe atopic dermatitis. Topical Tacrolimus Ointment is available in 2 strengths, 0.1% for adults and 0.03% for adults and children aged 2 years and older.
- Pimecrolimus cream, 1% is a calcineurin inhibitor immunosuppressant indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. It is not indicated for use in children less than 2 years of age. It is available in the US as Elidel®.

Other treatments in atopic dermatitis

- UV-A, UV-B, a combination of both, psoralen plus UV-A (PUVA), or UV-B1 (narrow-band UV-B) therapy may be used.
- In patients with severe disease and particularly in adults, phototherapy, methotrexate (MTX), azathioprine, cyclosporine and mycophenolate mofetil have been used.
- Hydroxyzine and diphenhydramine hydrochloride
- Barrier repair moisturizers
- Bleach baths
- Probiotics

ABOUT STUDY DRUG:

Pimecrolimus cream, 1% is a calcineurin inhibitor immunosuppressant indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.[16]

Dosage & Administration

Patients should apply a thin layer of pimecrolimus cream, 1% to all affected skin areas twice daily. Continuous long-term use of pimecrolimus cream, 1% should be avoided, and application should be limited to areas of involvement with atopic dermatitis. The safety of pimecrolimus cream, 1% under occlusion, which may promote systemic exposure, has not been evaluated. Use of pimecrolimus cream, 1% with occlusive dressings should be avoided.[16]

Warning and Precautions[16]

Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors, including Elidel® Cream, 1%. Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including Pimecrolimus Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- Pimecrolimus Cream, 1% is not indicated for use in children less than 2 years of age. Pimecrolimus Cream, 1% should not be used in immunocompromised adults and children, including patients on systemic immunosuppressive medications.
- If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be reexamined by their healthcare provider and their diagnosis be confirmed.
- The safety of Pimecrolimus Cream, 1% has not been established beyond one year of non-continuous use.

Common Side Effects

Anaphylactic reactions, ocular irritation after application of the cream to the eye lids or near the eyes, angioneurotic edema, facial edema, skin flushing associated with alcohol use and skin discoloration.

The use of Pimecrolimus Cream, 1% may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of Pimecrolimus Cream, 1% application and typically improve as the lesions of atopic dermatitis resolve.

Drug Interactions

Potential interactions between Pimecrolimus Cream, 1% and other drugs, including immunizations, have not been systematically evaluated. Due to low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

1.1 Study Rationale

Atopic dermatitis (eczema) is a common skin disorder that affects an estimated 35 million Americans, most often beginning in infancy and childhood. The introduction of topical calcineurin inhibitors for the treatment of atopic dermatitis addresses a clear unmet medical need by offering an important alternative to topical corticosteroids for patients, care-givers and physicians.

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease that affects a large part of the population. Although atopic dermatitis responds well to twice daily mid-strength corticosteroids, it is not optimal to expose a patient to the long term use of topical corticosteroids because of their side effects like skin atrophy, striae, tachyphylaxis, adrenal suppression, bacterial infections, and contact allergies. Pimecrolimus Cream 1% is an alternative topical therapy for use in patients with mild to moderate atopic dermatitis.

The purpose of the study is to establish the bioequivalence of Pimecrolimus Cream, 1% with that of Elidel® (pimecrolimus) Cream 1% in patients with AD using clinical endpoints. The double blind parallel group randomized placebo controlled study design was chosen as an appropriate study design based on the recommendations from draft guidance on bioequivalence study for Pimecrolimus Cream, 1% and from prescribing information for Elidel® (pimecrolimus) Cream 1%.

This trial uses the dose that has proven efficacy and safety in various clinical trials and approved strengths by developed countries.

As per FDA guidelines for Pimecrolimus, 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.

The study will commence after a written approval obtained from the IRB at respective sites. The study will be conducted as per the ICH-GCP (step 5) Guidelines and in accordance with the Declaration of Helsinki, (Fortaleza, Brazil, October, 2013).

1.2 Risk-Benefit Assessment

Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy have been reported in patients treated with topical calcineurin inhibitors, including Elidel® Cream 1%.

Participation in this study may or may not benefit the subjects. The expected potential benefits of Pimecrolimus include improvement in signs and symptoms of AD.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary Objective is to establish the bioequivalence between test drug, Pimecrolimus Cream, 1% with that of reference listed drug, Elidel® (pimecrolimus) Cream 1%, listed as RLD in the Orange Book (NDA No. N021302), in the treatment of mild to moderate AD, using the primary endpoint in the Per Protocol population, as detailed in FDA Draft Guidance on Pimecrolimus 1% Topical Cream dated March 2012.

2.2 Additional Objectives

- To establish superiority of each active treatment over the placebo using the primary endpoint in the modified intent to treat (mITT) population and Last Observation Carried Forward (LOCF)
- To assess individual signs and symptoms of Atopic Dermatitis (i.e., erythema, induration/papulation, lichenification and pruritus) in each treatment group
- To compare the safety and tolerability between the test and reference drugs

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Data Collection

The study is a randomized, double blind, active and placebo controlled, prospective multicenter, comparative therapeutic equivalence study in subjects with mild to moderate AD. The study consists of three treatment arms. As per FDA recommendations, this study will be a bioequivalence study with a clinical endpoint in the treatment of mild to moderate atopic dermatitis comparing the test product versus the reference listed drug 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 at the end of treatment (study Day 15).

A placebo control arm (vehicle of test product) is used 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.

The study duration for each subject is up to 32 days. There is a screening period of up to 14 days and a treatment period of 14 (± 3) days.

A total of 648 subjects will be included in the study. The subjects will be randomized into three groups in 1:1:1ratio.

The study consists of a total of 4 visits:

1. V1-Screening Visit, if required (-up to 14 days). If one is already using bland emollient (e.g Cetalphil® Lotion) continuously for 7 days, there is no need to be dispensed study bland emollient. In such case, procedures of Visit 1 (V1) and Visit 2 (V2) can be combined in one visit, if desired.
2. V2-Baseline and Randomization Visit (Day 1)
3. V3-Interim Visit (Day 8 ± 3 days)
4. V4-End of Therapy Visit (Day 15 ± 3 days)

It is strongly preferred to have one evaluator for each of the visits per subject. A back up evaluator may be present at baseline in case the primary evaluator is unavailable at follow up.

3.1.1 Visit 1 - Screening Visit (-up to 14 days)

3.1.1.1 Informed Consent and Assent (Assent as applicable):

During the informed consent and assent process, complete information about the study, study procedures, potential risk and benefits, alternative treatments and study drug information will be provided to the subject and/or guardian, as applicable. The subject and/or guardian will have sufficient time to consider the study aspects and ask questions. If the subject and/or guardian agree to participate in the study, they will confirm such via the study specific, IRB approved informed consent and assent (if applicable) form(s) and will receive a copy of such signed consent/assent form. All study related procedures will be undertaken, after obtaining informed consent from the subjects or guardian as applicable. Please see section 4.4.3 for additional details.

3.1.1.2 **Demographics:** Data including gender, birth date, age, ethnicity and race, body weight, height, and use of birth control (for females) will be recorded.

3.1.1.3 **Medical History**: Detailed medical history, including the start date of atopic dermatitis will be obtained. (Subject/guardian may verbally report signs and symptoms of atopic dermatitis with an onset at least 3 months prior.)

3.1.1.4 **Vital Signs:** Body temperature, blood pressure, and pulse rate will be performed and recorded.

3.1.1.5 **Diagnosis**: Subjects will undergo a clinical examination for the diagnosis of AD using the Hanifin Rajka criteria as outlined in Appendix I.

3.1.1.6 **Signs and Symptoms:** Signs and Symptoms of Atopic Dermatitis will be scored per body region (Head and Neck; Trunk; Upper Limbs; Lower Limbs). Signs and symptoms of AD (i.e., erythema, induration/papulation, and lichenification) will be scored objectively and recorded using the scale mentioned in Appendix II. The average/typical severity per sign/symptom of all lesions in the reported body region will be recorded.

Signs and Symptoms will be scored by the principal investigator or a qualified person delegated by the investigator. It is strongly preferred to have one evaluator for each of the visits per subject. A back up evaluator may be present at baseline in case the primary evaluator is unavailable at follow up.

The evaluator will score the sign and symptom per body region as it presents itself at the current visit, and not in comparison to any other visit.

3.1.1.7 **Body Surface Area (BSA) Assessment**: An overall body surface area involved with atopic dermatitis will be assessed. The palmar method (surface area of the palm including fingers and thumb is considered roughly equal to 1% of body surface area) is recommended for assessment. Subjects must have at least 5% BSA to be included in the study.

3.1.1.8 **Investigator's Global Assessment (IGA)**
At each visit, the investigator will assess the overall status of the subject's skin for AD using the IGA as per the scale noted in Appendix III. The IGA is a static assessment of how the subject's overall skin is observed at the time of the current visit. Scores or severity from prior visits should not be considered. The IGA scores for each visit will be documented on the source and the Case Report Form. Subjects must have a score of mild to moderate AD on IGA in order to be enrolled in the study.

3.1.1.9 **Pruritus Assessment**: Pruritus will be assessed by questioning the subject or the subject's guardian regarding the intensity of overall itching/scratching/discomfort in the 24 hours prior to the visit using the scale mentioned in Appendix II.

3.1.1.10 **Local Application Site Reactions**: Subjects will also be assessed at screening for evaluation of pre-treatment local application site reactions. At each study visit, the investigator will evaluate any application site reactions with separate severity scores for dryness, burning/stinging, erosion, edema, and pain. At each visit the reactions will be

noted and classified as mild, moderate or severe. Refer to Appendix IV Local Irritation Scale (LIS) for scoring of application site reactions.

3.1.1.11 **Physical Examination**: Subjects will undergo a general physical examination. A detailed dermatological examination is required. A full body dermatologic examination will assess if the subject has any dermatologic malignancies. If the subject does have a dermatologic malignancy, they should not be enrolled. The following systems should also be evaluated: head, ears, nose, throat, eyes, central nervous system, respiratory, cardiovascular, gastrointestinal, and musculoskeletal.

3.1.1.12 **Concomitant Medication:** History concomitant medications used will be obtained for at least the past 30 days. The start and stop date of medication use will be collected in addition to the reason for use. See section 6.3.

3.1.1.13 **Screening Criteria:**

Subjects will be evaluated to confirm that they meet the following screening criteria.

- Non-immunocompromised male or female aged 8 years and older
- Clinical diagnosis of mild to moderate atopic dermatitis (AD), as defined by the criteria of Hanifin and Rajka
- Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.)
- An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3)
- Affected area of AD involvement at least 5% body surface area (BSA)
- Expected to be able to meet inclusion and exclusion criteria (See section 4.1.) after minimum 7 days of continuous treatment with a bland emollient (e.g. Cetaphil® Lotion).

3.1.1.14 **Bland emollient distribution**: Subjects who meet Screening Criteria will receive a bland emollient (e.g. Cetaphil® Lotion) to use at least once per day over seven days. Those subjects who have already been using bland emollient as standard of care don't need study bland emollient dispensation. In such case, procedures of Visit 1 (V1) and Visit 2 (V2) can be combined in one visit, if desired.

3.1.1.15 **Schedule Next Visit**: Subjects will be instructed on care until their next visit. Subjects should return the provided bland emollient at the next visit. Subjects should be advised that they will be evaluated again at the next visit to confirm their eligibility for study treatment.

3.1.2 V2 - Baseline and Randomization Visit (Day 1)

The study specific procedures to be evaluated at baseline visit are:

3.1.2.1 Vital signs (See section 3.1.1.4)

3.1.2.2 Signs and symptoms evaluation (See section 3.1.1.6)

3.1.2.3 Body surface area assessment (See section 3.1.1.7)

3.1.2.4 Investigator's Global Assessment (IGA) (See section 3.1.1.8)

3.1.2.5 Pruritus Assessment (See section 3.1.1.9.)

3.1.2.6 Local application site reactions (pre-treatment) (See section 3.1.1.10)

3.1.2.7 **Urine pregnancy test** will be conducted for female subjects of child bearing age prior to dosing.

3.1.2.8 **Adverse Event Assessment**: Subjects will be questioned regarding adverse events in the form of non-leading questions (e.g., "How are you feeling?"). All adverse events will be assessed and documented and will be managed as per standard of care.

3.1.2.9 Concomitant medication (See section 3.1.1.12)

3.1.2.10 **Bland emollient collection:** Subjects will return with the bland emollient used over the past 7 days. The site staff will collect such as the subject should not use it while being treated with the study treatment.

3.1.2.11 Inclusion / Exclusion Criteria Evaluation (See section 4.1.)

3.1.2.12 **Randomization:** Subjects fulfilling inclusion and exclusion criteria will receive study product from the next available sequential randomized kit which contains one of the following three treatment arms:

- Test drug: Pimecrolimus Cream, 1%
- Reference listed drug: Elidel® (Pimecrolimus) Cream 1%
- Placebo: Vehicle of the test drug cream without Pimecrolimus

Each study product kit will contain three 100 gram tubes of study cream from the same randomized treatment arm. The kits will be packaged in a block size of 6. Each block will contain 2 kits of each treatment arm (2:2:2).

3.1.2.13 **Study Drug Dispensing:** Study drug tube(s) will be dispensed to each subject by a staff member delegated by the PI. The study drug dispenser will not participate in any clinical assessments. The delegated staff member will tear off the perforated label prior to dispensing to the subject. The perforated portion of the label contains the blinded treatment arm underneath an occlusive layer. The perforated label with blinded code will remain at the clinic site in case of emergency. (See section 6.5 regarding emergency unblinding.) The delegated staff member will dispense at least one tube of study cream.

Subjects (or guardians) will be instructed to apply a thin layer to the affected areas twice daily for 2 weeks (14 days). Subjects/guardians will be instructed about the following: 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. Caregivers who are pregnant, breastfeeding or may become pregnant should consult their physicians and follow their recommendations relating to the potential exposure to Pimecrolimus 1% Cream. Appendix V Instructions for the Patients will be reviewed with the subject or guardian.

The subject will be instructed to return all tubes to the study clinic.

3.1.2.14 **Diary Card Instructions / Schedule Next Visit**: Subjects or their guardians will be issued a diary card with instructions to record all applied and missed doses.

3.1.3 V3 - Follow up visit (Day 8 ± 3 days)

Subjects will return to the study site on day 8 with diary card. During this visit, the following procedures and evaluations will occur.

3.1.3.1 Signs and symptoms evaluation (See section 3.1.1.6)

3.1.3.2 BSA assessment (See section 3.1.1.7)

3.1.3.3 Investigator's global assessment (IGA) (See section 3.1.1.8)

3.1.3.4 Pruritus Assessment (See section 3.1.1.9.)

3.1.3.5 Local application site reactions (See section 3.1.1.10)

3.1.3.6 Adverse event assessment (See section 3.1.2.8)

3.1.3.7 Concomitant medication (See section 3.1.1.9)

3.1.3.8 **Assessment of Compliance:** The treatment diary card will be used to verify compliance. Compliance is defined in the term of study drug dose applied i.e. subject should apply the cream twice daily. The subjects should be using at least 75% and no more than 125% of expected study drug doses. If this is not the case, please decide if further study participation is recommended or if the subject should be re-instructed on proper study cream use and continued in the study.

3.1.3.9 **Study Drug Collection and Dispensing:** The delegated staff member will collect the used tube(s) from the subject. The used tube may be re-dispensed to the subject until fully used. A new tube from the subject kit may be provided if necessary. The subject should be reminded to return to the study clinic with all tubes at the next visit. Accountability of the dispensing of tubes will be recorded.

3.1.3.10 Diary Card Instructions / Schedule Next Visit (See section 3.1.2.13.)

3.1.4 V4 - End of Therapy Visit (Day 15 ± 3 days)

At the end of 2 weeks, subjects will return to the study site with treatment diary card for the end of therapy visit. During this visit, the following procedures and evaluations will occur.

3.1.4.1 Vital signs (See section 3.1.1.4)

3.1.4.2 Urine pregnancy test (See section 3.1.2.6)

3.1.4.3 Signs and symptoms evaluation (See section 3.1.1.6)

3.1.4.4 BSA assessment (See section 3.1.1.7)

3.1.4.5 Investigator's global assessment (See section 3.1.1.8)

3.1.4.6 Pruritus Assessment (See section 3.1.1.9.)

3.1.4.7 Local application site reactions (See section 3.1.1.10)

3.1.4.8 Adverse event assessment (See section 3.1.2.8)

3.1.4.9 Concomitant medication (See section 3.1.1.9)

3.1.4.10 Assessment of compliance (See section 3.1.3.8)

3.1.4.11 Study Drug Collection: The delegated staff member will collect all used and unused tube(s) from the subject.

3.1.4.12 Diary card Collection: The delegated staff member will collect the completed diary card from the subject.

3.1.5 Unscheduled Visits and Early Discontinuation Visit

An unscheduled visit is allowed at any time, for any reason, if in the investigator's opinion it is warranted. If the unscheduled visit is due to an AE, the investigator will determine whether additional visits are needed.

If a subject is discontinued from the study during an unscheduled visit, the unscheduled visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 4 will be performed.

3.2 Schedule of events

Details	**Screening**	**Baseline & Randomization**	**Follow up**	**End of therapy[#]**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**
Week	NA	NA	End of week 1	End of week 2
Day/s	(0-14 days)	(Day 1)	(Day 8)	(Day 15)
Window period	0-14 days	NA	± 3 days	± 3 day
Informed consent	**X**			
Detailed medical history	**X**			
Physical examination[##]	**X**			
Vitals**	**X**	**X**		
Establish diagnosis of AD	**X**			
Urine pregnancy test*		**X**		**X**
Inclusion and exclusion criteria	**X**	**X**		
Signs and Symptoms, Overall Body Surface Area, Investigator's Global Assessment, Pruritus	**X**	**X**	**X**	**X**
Application Site Reactions	**X**	**X**	**X**	**X**
Dispense bland emollient	**X**			
Collect bland emollient		**X**		
Dispensing of study drugs		**X**	**X**	
Issue of patient diary		**X**	**X**	
Assessment of drug compliance			**X**	**X**
Assessment of AEs		**X**	**X**	**X**
Review of concomitant medications	**X**	**X**	**X**	**X**
Collection of used and unused study drug tubes and completed patient diary			**X**	**X**

*Urine pregnancy test for females in child bearing potential age only
** Pulse rate, blood pressure and body temperature
[#] Schedule of events performed for end of treatment is applicable for early termination
[##]Physical examination: Head, ears, nose and throat, eyes, central nervous system, respiratory system, cardiovascular system, gastrointestinal system, musculoskeletal system and a detailed dermatological examination

3.3 Evaluation Criteria

3.3.1 Primary Endpoint:

The primary endpoint is the proportion of subjects 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 at the end of treatment (week 2 visit; study Day 15).

3.3.2 Secondary Endpoints:

- 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) are considered supportive information
- Application site reactions will be compared between treatment groups.

3.3.3 Safety Endpoints:

The type of AE(s), number of AE(s) and proportion of subjects with AE(s).

Safety assessment through the incidences and severity of all adverse events (AEs) reported during the study will be summarized by treatment group.

Subjects will be asked about any changes in their health since the prior visit. As such, AE(s) monitored using information volunteered by the subject and as observed by the PI will be categorized descriptively by total number of AE(s) based on their causality, as well as severity and compared between the 3 study arms.

4 STUDY POPULATION

4.1 Subject Selection

4.1.1 Inclusion Criteria

a) Non-immuno compromised male or female aged 8 years and older
b) Clinical diagnosis of mild to moderate AD, as defined by the criteria of Hanifin and Rajka (Appendix I)
c) Failed to respond adequately to other topical prescription treatments for AD, or for whom those treatments are not advisable. (The subject/guardian's verbal report of failure to other topical prescription treatments for AD will be adequate.)
d) A diagnosis of AD for at least 3 months (Subject/guardian may verbally report signs and symptoms of atopic dermatitis with an onset at least 3 months prior.)
e) An Investigator's Global Assessment (IGA) of disease severity of mild or moderate at baseline (score of 2 or 3)
f) Affected area of AD involvement at least 5% body surface area (BSA)
g) Treated with a bland emollient (e.g. Cetaphil® Lotion) for at least 7 days continuously
h) Willing and able to give written informed consent (and assent as applicable) and willing to comply with the trial protocol
i) If female of childbearing age, willing to use an acceptable form of birth control, that is stable for at least 3 months prior to baseline and throughout the study. Acceptable forms of birth control include any of the following: (1) hormonal birth control, which must be stable for > 3months prior to baseline; (2) abstinence; subject must use condom plus spermicide, if becomes sexually active; (3) double barrier method, such as condom plus spermicide.

4.1.2 Exclusion 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, impetigo).
c) Sunburn, extensive scarring or pigmented lesion(s) in any treatment area at baseline, which would interfere with evaluations
d) History or presence of confounding skin conditions, e.g., psoriasis, rosacea, erythroderma, ichthyosis, or scabies.
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) Concurrent disease or treatment likely to interfere with the study treatment or evaluations
g) Use within one month prior to baseline of
   - Oral or intravenous corticosteroids (Subjects on stable and continued doses of nasal, or inhaled corticosteroids for conditions other than atopic dermatitis may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study. Ophthalmic corticosteroids are not excluded.)
   - UVA/UVB therapy
   - PUVA (psoralen plus ultraviolet A) therapy
   - Tanning booths
   - Nonprescription UV light sources
   - Immunomodulators or immunosuppressive therapies
   - Interferon
   - Cytotoxic drugs
   - Tacrolimus
   - Pimecrolimus
h) Use within 14 days of baseline of
   - Systemic antibiotics
   - Calcipotriene or other vitamin D preparations
   - Retinoids
i) Use within 7 days prior to baseline of
   - Systemic antihistamines (Subjects on a stable and continued dose of systemic antihistamines may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study.)
   - Topical antibiotics
   - Topical corticosteroids
   - Other topical drug products
   - Probiotics
j) 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 (e.g. Cetaphil® Lotion).

k) Known allergy or hypersensitivity to pimecrolimus or any other component of the test product or RLD
l) Not willing to minimize or avoid natural and artificial sunlight exposure during treatment
m) Currently enrolled in an investigational drug or device study or used an investigational drug or investigational device treatment within 30 days prior to first application of the test article

4.2 Withdrawal of Subjects

A subject will be discontinued from the study under the following circumstances:

- If the subject requests discontinuation or withdraws consent
- If a subject experiences a serious adverse event that renders them incapable of further participation in the study
- Any entry criteria are violated and the violation becomes apparent during the course of the study

In the event of withdrawal of a subject, the Investigator should assess the primary cause for the subject's withdrawal and document this in the Case Report Form (CRF). As far as possible all subjects should undergo all end of therapy visit assessments.

Subjects will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care. Any withdrawal must be fully documented in the CRF and source documents. The Investigator may also withdraw a subject at any time if this is considered to be in the subject's best interest.

The subject will be discontinued from the study if the inclusion and exclusion criteria are not met, has withdrawn the informed consent, has not been compliant with the study medication, or if the Investigator considered such in the best interest of the subject due to an AE.

4.3 Protocol Deviations and Violations

After a subject is enrolled into the study and is noticed to be noncompliant with inclusion and exclusion criteria, the same will be documented as a Protocol Violation(s).

During the conduct of the study process if deviation(s) are noticed from the norm mentioned in the protocol, the same will be documented as Protocol Deviation(s).

The severity of the protocol deviation will be graded as minor if the deviation is not altering the integrity of the study plan or its safety and efficacy outcome, as major if the deviation is altering the integrity of the study plan or its safety and efficacy outcome.

Sponsor reserves the right to terminate the study at any time and bears the responsibility for informing applicable regulatory authorities. Whereas the investigator reserves the right to discontinue the study for safety reasons at any time and bears the responsibility to inform the IRB.

All violations or deviations from the approved protocol would be documented. The following details will be captured:

- Description of deviation
- Date of deviation
- Date reported

In case of a deviation, the investigator will inform CRO/Sponsor and seek approval for continuation/discontinuation of the concerned subject. The investigator should not deviate from the protocol. CRO will not assume any resulting responsibility or liability from unapproved deviations. The IRB will be informed of protocol deviations by the investigator, according to applicable regulations and the IRB's established procedures.

4.4 Ethical and Regulatory Considerations

4.4.1 Declaration of Helsinki and ICH-GCP

The study will be conducted according to the protocol and to guidelines from the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) in clinical trials and in compliance with all relevant local guidelines. Written approval will be obtained from the IRB prior to recruitment of subjects into the study and for all relevant material like the protocol, written subject information and informed consent form prior to recruitment into the study.

4.4.2 Protocol Amendments

Proposed amendments to the protocol and aforementioned documents would be submitted to the sponsor / CRO for review and approval, and then to the IRB, as necessary. Amendments may be implemented only after a copy of the IRB approval letter has been transmitted to the sponsor. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving sponsor or IRB approval.

4.4.3 Informed Consent and Assent

The written consent and assent document will embody the elements of informed consent and assent as described in the Declaration of Helsinki, and will also comply with local regulations. The principles of informed consent will be implemented before protocol specified procedures or interventions are carried out. Information will be given in written form. Subjects, their relatives, guardians, if necessary legal representatives will be given ample opportunity and time to discuss any details of the study with trained local personnel.

The Investigator will ensure that the subject has been given enough information, both written and oral, about the nature, possible risks, benefits and procedures that the study will entail, in a language that the subject can understand. They will be informed that participation is purely voluntary and withdrawal at any time is possible and that

non-participation in the study will in no way affect their medical treatment. Ample time will be given for questions, discussion, and consideration.

Informed Consent Forms (ICF) / Assent will be, in a language fully comprehensible to the prospective subjects and be completed by the subject with assistance if requested from trained local personnel. Informed consent / assent shall be documented by the use of written consent form approved by the IRB and signed by the subject. The dated signature of the subject will be documented in the informed consent form. The signature confirms the consent is based on information that has been understood. The investigator, for possible inspection by regulatory authorities and/or CRO and regulatory compliance, will maintain each subject's signed informed consent form. A copy of the informed consent/assent forms will be given to the subject/parent/guardian and the original will be retained in the records of the investigator. Site will take an acknowledgement from the subject in the source document that the subject has received a copy of the completed and signed ICF / Assent from the site.

4.4.4 Patient Information Sheet

All subjects will be provided a signed copy of the informed consent that details the study procedures, the risk and benefits of the study, emergency contact numbers, procedures to be followed, voluntary participation and withdrawal, compensation etc. The informed consent will be provided in a language fully comprehensible to the prospective subjects.

5 INVESTIGATIONAL PRODUCTS

The investigational products to be used for this study are:

- Test drug: Pimecrolimus Cream, 1%
- Reference listed drug (RLD): Elidel® (Pimecrolimus) Cream 1%
- Placebo: Vehicle cream

5.1 Packaging, Labeling and Storage of Investigational Products

Sponsor will supply the drugs used in this study. The drug will be manufactured complying with all the required regulations. The medication assigned to each subject will be determined by a randomization list generated in SAS by a statistician of the CRO. The investigational product will be labeled and packaged accordingly.

The following general information will be provided on the clinical trial supply label:

- **Caution: New Drug - Limited by Federal (or United States) law to investigational use**
- Study CD-14-875

- Kit # XXXX
- Elidel® Cream, or Pimecrolimus Cream 1%, or Placebo Cream
- Renaissance Pharma, Inc.
- Store at 25°C (77°F);. excursions permitted to 15°C to 30°C (59°F to 86°F) Do not freeze.
- Keep out of the reach of children.
- Rx only.
- FOR TOPICAL USE ONLY.
- NOT FOR OPHTHALMIC USE.
- Apply a thin layer of cream to the affected skin twice daily.

The investigational products would be stored in a secured area that is access controlled and remains within the storage conditions mentioned in the product label or specified by the sponsor. Access to investigational products will be provided only to the pharmacist or authorized personnel.

5.2 Retention of Study Records and Drug Samples

Retention of study drug samples will be done as per the guidelines presented in '21 CFR 320.38, 320.63' and the FDA Guidance for Industry, "Handling and Retention of BA and BE Testing Samples." Randomized kits for subject use will be randomly selected from the drug supplies received prior to dispensing to subjects. The sponsor will instruct separately on the amount of kits required to be kept as bioequivalence samples and will not be returned to the sponsor at any time.

Records of bioequivalence testing will be maintained as per '21 CFR 320.36' guidelines. In addition, the investigators will 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).

5.3 Dispensing

The investigational products will be dispensed as tubes from kits received and in ascending order by the pharmacist or designee to the investigator/ delegated personnel. See section 3.1.2.12.

5.4 Drug accountability

Relevant forms will be provided to the investigator and the pharmacist/designee to maintain accurate written records of all investigational product from sponsor, dispensed to subjects and returned. At the end of the study the drug (with the exception of bioequivalence retention kits) will be returned to the sponsor and reconciliation of records will be performed.

6 TREATMENT OF STUDY DRUG

6.1 Randomization

Randomization will be performed using SAS® package (SAS Institute Inc., USA, Version 9.2 or higher).

Study kit numbers will be randomly assigned to one of the three treatment arms based on a randomization code list. The statistician will generate the randomization code list; a copy of this list will be shared with the IP handling team.

6.2 Dosing and Administration Information

Dosage of the study drugs: Apply a thin layer of Cream to the affected skin twice daily. Rub in gently and completely. Subjects will be advised to wash their hands before and after application of drugs (unless the hands are being treated) and to avoid accidental exposure of drug with eyes, nose, mouth and other mucus membrane. The use of occlusive dressings or wrappings over the lesions should be avoided.

At any point of time, if there are signs or symptoms of intolerability or toxicity, the investigator, based on his/her medical discretion may delay further treatment with study medication, or terminate the subjects from further study participation. At the time of check out for visit 2 the subjects will be provided with sufficient amount of study medication and a treatment diary card. Subjects will be instructed to continue with the medications twice daily and contact the site if any problem arises. The used and unused medication tubes will be collected at the end of therapy visit at Day 8 and Day 15 visits.

6.3 Concomitant Medication

Current medications and any medications taken in the 30 days prior to the start of the study (Screening/Baseline, Visit 1) will be recorded as prior/concomitant medications with the corresponding indication and dose. Prescription and over-the-counter (OTC) medications, including NSAIDs will be recorded. All medications taken on a regular basis should be recorded prior to commencing the use of the test article. If concomitant medication is required during the study, subjects will be treated accordingly and a decision to continue or discontinue the subjects will be made by the investigator, based on the pharmacology and pharmacokinetics of the study product and the concomitant medication. All prescription and over the counter medications and vaccinations will be recorded and reported.

Subjects may continue during the study with the same cleansing regimen that they had prior to the study. If not medically required, any changes in such should occur after the study completion. Subjects should not use any moisturizers while using the study medication.

6.4 Prohibited Medications and Treatments

The following prescription and over-the-counter drug products, procedures and activities are prohibited during or the entire study:

- Treatment for atopic dermatitis, other than assigned treatment
- Topical or systemic corticosteroid, topical or systemic antibiotic, topical or systemic antifungal, topical antihistamine, immunosuppressive drugs (e.g. cyclosporine, methotrexate, or azathioprine), immunomodulator (e.g., tacrolimus), calcipotriene or other vitamin D preparations, retinoids, interferon
    - Subjects on stable and continued doses of nasal or inhaled corticosteroids for conditions other than atopic dermatitis may be enrolled at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study.
    - Ophthalmic corticosteroids are not excluded.
- Systemic antihistamines (Subjects on a stable and continued dose of systemic antihistamines may be enrolled and continued in the study at the investigator's discretion when the investigator considers that such will not affect the efficacy or safety evaluations of the study.)
- CYP3A inhibitor, e.g., erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers cimetidine, grapefruit or grapefruit juice
- Topical product, other than assigned treatment (e.g., sun screen, new brand of cosmetic or cleanser, cream, lotion, ointment, or powder) applied on or near the treatment area(s)
- Phototherapy, e.g., PUVA, UVA or UVB therapy
- Bathing, showering or swimming within 3 hours of applying study treatment
- Prolonged baths (i.e., longer than 5 minutes), excessive exposure to sunlight, or use of tanning booths, sunlamps or nonprescription UV light sources.
- Bleach baths
- Covering any treated area with bandage(s), dressing(s) or wrap(s)
- Allowing the study treatment to come in contact with the eyes, nose, mouth, vagina, or rectum (mucous membranes).
- Probiotics
- Vaccinations

Subjects who require prohibited interventions during the study will be withdrawn from the study. The use of concomitant and prohibited medications will be recorded on the concomitant medications section of the CRF.

6.5 Blinding and Unblinding

Blinding:

This study will be conducted as a double-blind study. Subjects in three arms will receive either study medications or placebo from subject kits (IMP Kit) which are identical and labeled in a manner to maintain the blind.

Subjects entering the study will be randomized in ratio of 1:1:1 for 3 treatment arms.

Knowledge of the randomization list will be limited to the persons responsible for the creation of the randomization list, labeling, packing & distribution of the IMP's.

Randomization schedule will be generated based on the randomization request details and study design outlined in the protocol using SAS by the statistician & will be used to assign subjects to treatment groups. Randomization schedule will be shared with the unblinded team involved in labeling, packaging, distribution of investigational products by the statistician. Unblinded personnel at packaging site will pack the IMP's based on the randomization schedule. All the IMP's will be identified with their respective kit numbers.

To maintain the blinding through packaging:
a. Packing material should be similar in colour and size.
b. Labelling and packaging shall be performed as per the instructions given in the batch packaging document.
c. Uniformity shall be maintained during assembly of labels on units, placement of units in the carton & sealing of the subject kits.

IMP's will be distributed to sites along with corresponding respective blinded labels containing the randomized treatment.

Site personnel will pick the appropriate next numbered IMP kit and complete the details on the IMP tube label dispensed. Site personnel will dispense to the subject/guardian specific IMP tube(s) and instruct the subject/guardian on the IMP usage. Subjects/guardians are advised to return the used & unused IMP tubes.

Unblinding:
In the case of an emergency, the investigator may learn the treatment arm the subject was randomized to by removing the occlusive tube label remaining in the subjects records stored at the investigator's site. Except in the circumstances detailed in unblinding section (breaking the blind), the code will not be broken. The CRO shall be contacted before unblinding whenever possible.

Unblinding a subject's treatment is restricted to emergency situations and should only be done to facilitate the proper care of a subject. In-case of emergency, investigator/authorized personnel will contact the CRO for unblinding the subjects by submitting the Un-blinding Request Form. The investigator should always attempt to contact the medical monitor/designee before breaking the blind.

In case of safety issues, a medical emergency where the identity of investigational product is essential for medical management of a subject, or an AE/SAE that requires expedited reporting, shall a subject become un-blinded as to the treatment they are receiving. The un-blinding provides the information about the identity of study drug provided to the subject as per the randomization list.

If there is a medical emergency with a subject, the Study PI will take the necessary medical action to address the emergency first, and then send an unblinding form to the unblinded person at CRO. Unblinded person sends this form to the medical monitor/designee for approval. If the medical monitor or designee, after careful consideration of the circumstances, feels that there is a need to know which treatment group the subject is in, he/she will approve the unblinding by signing this form. This signed /approved form will be sent to the site, upon which investigator can unblind the subject. Based on the authorization from the unblinded authority of CRO, the study PI will access to unblind the particular subject ID.

Should the unblinding happen, the same treatment kit should be withdrawn from the subject. The kit should be quarantined with proper status on site.
An account of all broken or unbroken codes will be collected by the monitor at or after site closure.

Every attempt will be made to maintain the blinding throughout the study. In any case treatment code is broken; the un-blinding procedure must be adequately documented in the subject's study file.

Before breaking the blind of an individual subject's blinded treatment, the investigator should have determined that the information is necessary, i.e., that it will alter the subject's immediate management. Every attempt will be made to maintain the blind throughout the study.

If the treatment blind is broken, the investigator will record the reason and date, time on the appropriate CRF. If the blind is broken because of an AE/SAE, an AE/SAE form will be completed and informed to CRO. Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial after database lock.

7 SAFETY ASSESSMENT

Adverse event (or adverse experience, AE): Any untoward medical occurrence in a subject or clinical investigation subject administered the test and reference product which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including for example an abnormal laboratory finding), symptom or disease temporally associated with the use of the test and reference

product, whether or not considered related to the test and reference product. Each subject will be carefully monitored for the development of any adverse events. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of the study personnel or spontaneous reports from the subjects.

Subjects will be monitored for safety and tolerability during the study and until the completion of the study. Any AEs, including either observed or volunteered problems, complaints, signs or symptoms, occurring during the course of the study or designated follow-up periods, must be recorded on the subject's CRF. This would include AEs resulting from concurrent illnesses, reactions to concomitant medications.

Each AE will be evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). Additionally, the actions taken (e.g., discontinuation of study medication, administration of treatment) and the resulting outcome of the AE should be indicated on the CRF.

Any subject who is withdrawn from the study due to an adverse event should be followed until the outcome of the event is determined, and the investigator will prepare a written summary of the event and document the available follow-up information in the study documents.

7.1 Intensity of Adverse Events

The intensity of the AEs will be graded according to the following criteria:
a. Mild: Events that are usually transient; require only minimal treatment or therapeutic intervention; do not generally interfere with usual daily activities.
b. Moderate: Events that are alleviated with additional specific therapeutic intervention; interfere with usual daily activities, causing discomfort but pose no significant or permanent risk or harm to the subject.
c. Severe: Events that require intensive therapeutic intervention; interrupt usual daily activities, or significantly affect clinical status; pose a significant risk or harm to the subject and hospitalization may be required.

7.2 Causality Assessment

Causality denotes the relation of the event to the study drug and is classified as follows by the investigator:
a. 'Definitely Related' when the AE is clearly related to the study drug or intervention and is defined as meeting all the following conditions:
Has a reasonable temporal relationship to the investigational agent(s) or research intervention; could not have been readily produced by the subject's clinical state or have been due to environmental or other intervention; disappears or decreases with reduction in investigational agent or cessation of intervention; recurs with re-exposure to the

investigational agent(s) (in case of studies involving multiple administration of drug); no alternative cause is present; follows a known pattern of response to intervention

b. 'Probably Related' when the AE is likely related to the investigational agent(s) or intervention and is defined as meeting any three of the following conditions:
Has a reasonable temporal relationship to the investigational agents(s) or research intervention; Could not readily have been produced by the subject's clinical state or have been due to environmental or other intervention; Follows known or suspected pattern of response to intervention; Disappears or decreases with reduction in investigational agent or cessation of intervention; Alternative cause may be present

c. 'Possibly Related' when it may be related to the investigational agent(s) or intervention and is defined as meeting any two of the following conditions:
Has a reasonable temporal relationship to the investigational agents(s) or research intervention; Could not have been produced readily by the subject's clinical state or have been due to environmental or other intervention; Follows known or suspected pattern of response to intervention; Alternative cause is present

d. 'Unlikely Related' when it is doubtfully related to the investigational agent(s) or intervention and is defined as meeting any two of the following conditions:
Has a temporal relationship to the investigational agents(s) or research intervention; Could readily have been produced by the subject's clinical state or have been due to environmental or other intervention; Does not follow a known pattern of response to intervention; Does not reappear or worsen with reintroduction of intervention (in case of studies involving multiple administration of drug); Alternative cause is present

e. 'Not related' when the AE is clearly not related to the investigational agent(s) or intervention and is defined as meeting all of the following conditions:
Has no temporal relationship to the investigational agents(s) or research intervention; Follows no known or suspected pattern of response; Alternative cause is present.

7.3 Frequency

i.If the same type of AE occurs only once will be documented as 'Single Episode'.
ii.If the same type of AE occurs more than once, will be documented as 'Recurrent'.
iii.If an AE is still continuing (not resolved) will be documented as 'Continuous Event'.

7.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any event that suggests a significant clinical hazard, contraindication, side effect, or precaution. This includes any event which:
- Results in death.
- Life threatening.
- Results in persistent or significant disability / incapacity.
- Requires repeated hospitalization or prolongation of existing hospitalization.

- Results in congenital anomaly / birth defect.
- Is an important medical event which includes other events, based on medical judgment, which jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.

The investigator or a suitable designee will record all adverse events observed, either queried or spontaneously reported by the subject(s).
The Serious Adverse Event Reporting will be in compliance with the local legal and regulatory requirements.

The adverse events will be followed until resolution or to the satisfaction of the investigator(s) unless the subject's is deemed lost to follow-up.

8 DATA HANDLING, RECORDING AND QUALITY ASSURANCE

8.1 Data Handling and Record Keeping

The investigator must ensure that proper source documentation for all activities performed in relation to this study are diligently maintained and securely kept. The investigator will transfer all relevant data from the source documents to the CRF as stipulated in this study protocol and his/her signature on the CRF guarantees the completeness and integrity of these data. All records and documents pertaining to the study will be maintained as documented for at least a period of 2 years following the date a marketing application is approved for the indication for which it is being investigated; or if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities are notified. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator / institution as to when these documents no longer need to be retained.

8.2 Access to Source Data

The investigator must ensure that institutional regulations and the informed consent form clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents by the sponsor, the sponsor's delegates, the US FDA, local regulatory bodies, or the IRB.

8.3 Source Data Verification and on-site Audits

Besides regular source data verification by the study monitor, regulatory authorities, the IRB, and/or the sponsor's personnel or designate may request access to all source documents, CRFs, and other study documentation for on-site audit inspections. The Investigator, who must provide support at all times for the activities, must guarantee direct access to these documents.

8.4 Monitoring

The study will be monitored by the CRO, Sponsor, and/or Sponsor Delegate. Monitoring may be done by personal visits by the site monitor who will review the CRFs and source documents, and/or by frequent communications (letter, email, telephone, and fax). The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

8.5 Data Management

Data management will ensure that clinical parameters collected on each subject throughout the study are as complete, accurate and of the highest quality possible and that the procedures are performed in accordance with all applicable guidelines and regulations (including ICH guidelines). CRFs, questionnaires and treatment diaries shall be made available to the data management site.

9 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The following information provides an overview of the issues related to the analysis of data collected during the study.

9.1 Determination of Sample Size

The primary statistical analysis of interest is the proportion of subjects in the PP population with a clinical response of treatment success (at least an Investigator's Global Assessment of Clear or Almost Clear) at study Day 15. Considering the pivotal studies of the Reference Listed Drug, it is assumed that the active test and RLD will have approximate success rates at 21% and the vehicle cream will have an approximate success rate of 9%. A sample size of 184 subjects per group will provide at least 99% power to demonstrate bioequivalence (i.e., the 90% confidence interval (Yates' continuity -corrected) of the absolute difference between the test and reference composite success rates is within a defined equivalence range [-0.20, +0.20]). Assuming the conversion rate from mITT to PP will be about 90%, 205 subjects in each of the groups of the mITT population will provide at least 85% power to demonstrate superiority of active over placebo. Under the above assumptions, the overall global study power to demonstrate bioequivalence and superiority is estimated to be approximately 85%. To allow for about 5% of subjects who may drop out from the study or are otherwise non-evaluable, approximately 648 subjects will be enrolled (216 in each active group and 216 in the placebo group).

9.2 Statistical Methods

9.2.1 Study Population

9.2.1.1 Intent-to-treat (ITT)

The safety population includes all randomized subjects who applied the study product at least once.

9.2.1.2 Modified Intent-to-treat (mITT)

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 evaluation visit.

9.2.1.3 Per Protocol (PP)

The PP population includes all randomized subjects who met all inclusion/exclusion criteria, applied 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 evaluation within the designated visit window (+/- 3 day) with no protocol violations that would affect the treatment evaluation. The subject's compliance will be verified by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.

9.2.2 Statistical analysis

9.2.2.1 Efficacy Analysis

Primary Efficacy Parameter:

Equivalence Analysis

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: $P_T - P_R < -0.20$ 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 T_n

${}_c n_T$ = number of successes in test treatment group T_n

n_R = sample size of reference treatment group R_n

${}_c n_R$ = number of successes in reference treatment group R_n

$\boldsymbol{P}_T = {}_c n_T / n_T$, $\boldsymbol{P}_R = {}_c n_R / n_R$,

and se = $(\boldsymbol{P}_T (1 - \boldsymbol{P}_T) / n_T + \boldsymbol{P}_R (1 - \boldsymbol{P}_R) / n_R)^{1/2}$.

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

$L = (\boldsymbol{P}_T - \boldsymbol{P}_R) - 1.645 \text{ se} - (1/n_T + 1/n_R) / 2$

$U = (\boldsymbol{P}_T - \boldsymbol{P}_R) + 1.645 \text{ se} + (1/n_T + 1/n_R) / 2$

We reject H_0 if $L < -0.20$ or $U > 0.20$

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

Superiority of the treatment:

Superiority of both treatments over the placebo will be evaluated for mITT population at week 2. Tests for superiority of each active treatment over the placebo will be conducted using two-sided Fisher exact test at the 5% level of significance.

The efficacy analysis will be conducted in mITT population and Last Observation Carried Forward (LOCF) approach will be used to impute for missing data in the mITT population.

Secondary Efficacy & Safety Parameters:

The 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) will be evaluated as supportive information.

The type of AE(s), number of AE(s) and proportion of subjects with AE(s)

Safety assessment through the incidences of all adverse events (AEs) reported during the study and summarized by treatment group.

Main Variables Assessed for Safety & Tolerability:

AE(s) monitored using information volunteered by the subject and as observed by the PI will be categorized descriptively by total number of AE(s) based on their causality, as well as severity and compared between the 3 study arms.

9.2.2.2 Safety Analysis

Subjects will be monitored for safety and tolerability throughout the study (as explained above) and until the completion of the study.

Adverse events will be tabulated for each and summary statistics will be statistically evaluated using Fisher's exact test.

9.3 Presentation of Results

Summary statistics will be presented for actual values and changes from the baseline. If the values are raw measurements or derived totals from raw measurements, then the statistical measures; mean and median will be presented to single decimal place more than the maximum number of decimal places to which the raw measurements are collected. Minimum and maximum will be presented to the same number of decimal places as the maximum of decimal places to which the raw measurements are collected.

Standard deviation (SD) will be presented two decimal places more than the raw data. If the values are derived values then an extra decimal place will be added to all these measures. Percentages will always be presented in two decimal place. Zero counts will be reported as '0' with '0.0%' percentages and 100 percentages will be presented as 100.00% counts will be presented as integer values.
Confidence intervals and percentiles will be presented with two decimal place. All p-values will be reported to four decimal points and p-values less than 0.0001 will be reported as <0.0001.

Interim Evaluation:
No interim evaluation is planned for this study.

9.4 Handling of Dropout or Missing Data

No missing imputations will be done for either efficacy or safety parameters estimations.
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 in the treated area requiring treatment should be discontinued, excluded from the PP population, but included in the mITT population, using LOCF.

10 STUDY ADMINISTRATIVE PROCEDURES

10.1 Regulatory Authority Approval

The Sponsor / CRO will obtain approval to conduct the study at each site from the relevant local regulatory authorities, in accordance with applicable regulatory requirements prior to initiating a site. The study will be performed in compliance with ICH-GCP guidelines and local guidelines.

10.2 Confidentiality of Subjects

The records of the subject's medical history, physical examination, clinical examination results and any other information or data generated during the study will be made available to the sponsor or its designees (auditors, monitors), ethics committee, and will be made available to the local drug regulatory bodies and other participating countries, formulary committees of hospitals, at the opinion of sponsor. A pre-condition for entry into this study will be subject's agreement to release all of the above-mentioned documentation and data for any lawful purpose.

10.3 Delegation of Investigator Responsibilities

The investigator will ensure that all persons assisting with the trial are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their trial related duties and functions. The investigator should maintain a list of co-investigators and other appropriately qualified persons to whom he or she has delegated significant trial related duties.

10.4 Study Termination and Site Closure

Upon completion of the study, the CRO will conduct the following activities in conjunction with the Investigator or site staff, as appropriate, including but not limited to the following:

- Return of all study data to the sponsor or sponsor authorization for safe and adequate disposition by the site
- Data queries
- Review of site study records for completeness

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but are not limited to, ethical issues or severe non-compliance. If the sponsor determines such action is needed, the sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect. The sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator must inform the IRB promptly and provide the reason for the suspension or termination. If the study is prematurely discontinued, all study data must be returned to sponsor.

10.5 Archiving and Record Retention

The investigator will maintain adequate records for the study, including medical records, laboratory reports (if any), signed informed consent forms, drug disposition records, correspondence with the IRB, adverse event reports and information regarding subject discontinuation and completion of the study. Laboratory investigation reports, logbooks and data forms based on in-house procedures will be the primary data collection documents for this study.

Study documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product by Sponsor. The Investigator/institution should take measures to prevent accidental or premature destruction of these following documents.

- Signed informed consent documents for all subjects

- Subject identification code list, screening log (if applicable), and enrolment log
- Record of all communications between the Investigator and the IRB
- Composition of the IRB
- Record of all communication between the Investigator and the CRO
- List of co-investigators and other appropriately qualified persons to whom the Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of CRFs, questionnaires, treatment diaries and of documentation of correction for all subjects
- All other source documents (subject records, hospital records, laboratory records, etc.)
- All other documents deemed relevant for this study from those listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the conduct of a clinical trial)

Normally, these records will be held in the investigator's archives. If the Investigator is unable to meet this obligation, he or she must ask the sponsor for permission to make alternative arrangements. Details of these arrangements must be documented.

10.6 Study Report and Publication Policy

The publication policy will be at the sole discretion of the Sponsor. If published the subjects identity will not be revealed.

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12 APPENDICES

12.1 Appendix I: Hanifin and Rajka Criteria

The diagnosis of atopic dermatitis using the Hanifin and Rajka criteria requires that subjects have the following: at least 3 of the 4 major criteria and 3 of the 23 minor criteria.

Major criteria: At least 3 or more of the following

- ☐ Pruritus
- ☐ Typical morphology and distribution
  - Facial and extensor involvement in infants and children
  - Flexural lichenificaiton or linearity in adults
- ☐ Chronic or chronically relapsing dermatitis
- ☐ Personal or family history of atopy
  - Allergic rhinitis
  - Asthma
  - Atopic dermatitis

Minor criteria: At least 3 or more of the following

- ☐ Anterior neck folds
- ☐ Anterior subcapsular cataracts
- ☐ Chelitis
- ☐ Course influenced by environmental or emotional factors
- ☐ Dennie-Morgan infraorbital fold
- ☐ Early age onset
- ☐ Facial pallor or facial erythema
- ☐ Food intolerance
- ☐ Keratoconus
- ☐ Ichthyosis, palmar hyperlinearity, or keratosis pilaris (Please note that ichthyosis is exclusionary.)
- ☐ Immediate skin test reactivity
- ☐ Intolerance to wool and lipid solvents
- ☐ Itch when sweating
- ☐ Nipple eczema
- ☐ Orbital darkening
- ☐ Perifollicular accentuation
- ☐ Pityriasis alba
- ☐ Raised serum IgE
- ☐ Recurrent conjunctivitis
- ☐ Tendency toward cutaneous infections (especially S. aureus and herpes simplex) or impaired-cell immunity
- ☐ Tendency toward nonspecific hand or foot dermatitis
- ☐ White dermatographism or delayed blanch
- ☐ Xerosis

12.2 Appendix II: Scoring of signs and symptoms in AD

Individual Signs and Symptoms of AD

Sign and Symptom	Score	Category	Definition
Erythema	0	None	No erythema present
	1	Mild	Slight erythema: very light-pink
	2	Moderate	Dull red, clearly distinguishable
	3	Severe	Deep/dark red
Induration/ Papulation	0	None	None
	1	Mild	Slightly perceptible elevation
	2	Moderate	Clearly perceptible elevation but not extensive
	3	Severe	Marked and extensive elevation
Lichenification	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
Pruritus	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

12.3 Appendix III: IGA Scoring

Investigator 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

12.4 Appendix IV: Local Irritation Scale (LIS)

Dryness	0 None	1 Mild	2 Moderate	3 Severe
Stinging/burning	0 None	1 Mild	2 Moderate	3 Severe
Erosion	0 None	1 Mild	2 Moderate	3 Severe
Edema	0 None	1 Mild	2 Moderate	3 Severe
Pain	0 None	1 Mild	2 Moderate	3 Severe

12.5 Appendix V: Instructions for the patients

WARNING: LONG-TERM SAFETY OF TOPICAL CALCINEURIN INHIBITORS HAS NOT BEEN ESTABLISHED

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream, 1%.
Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis.
- ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age.

ELIDEL Cream, 1% may cause serious side effects. It is not known if ELIDEL Cream, 1% is safe to use for a long period of time. A very small number of people who have used ELIDEL Cream, 1% have had cancer (for example, skin or lymphoma). However, a link with ELIDEL Cream, 1% use has not been shown. Because of this concern:

- A patient should not use the study cream continuously for a long time.
- Study cream should be used only on areas of skin that have eczema.
- A patient should not use sun lamps, tanning beds, or get treatment with ultraviolet light therapy during the study.
- A patient should limit sun exposure during the study and even when the study cream is not on the skin. If a patient needs to be outdoors after applying the study cream, the patient should wear loose fitting clothing that protects the affected area from the sun. The physician should advise the patient about other types of protection from the sun. It is not known how the study cream may affect your skin with exposure to ultraviolet light.
- A patient should not cover the affected skin with bandages, dressings or wraps. A patient can wear normal clothing.
- The study cream is for topical use on the skin only. Do not get the study cream in your eyes, nose, mouth, vagina, or rectum (mucous membranes). If you get the study cream in any of these areas, burning or irritation can happen. Wipe off any study cream from the affected area and then rinse the area well with cold water. The study cream is for external use only.
- Wash hands before using the study cream. When applying the study cream after a bath or shower, the skin should be dry.
- Apply a thin layer of the study cream only to the affected skin areas, twice a day, as directed by the physician. Use the smallest amount of cream needed.
- A patient should not bathe, shower or swim for at least 3 hours after applying the study cream. This could wash off the cream. In addition, please avoid prolonged bathing (i.e. longer than 5 minutes).

- If you apply the study cream to another person, or if you have eczema and are not treating your hands, it is important for you to wash your hands with soap and water after applying the cream. This should remove any cream left on your hands. Caregivers who are pregnant, breastfeeding or may become pregnant should consult their physicians and follow their recommendations relating to the potential exposure to Pimecrolimus 1% Cream.
- Do not cover the skin being treated with bandages, dressings or wraps. You can wear normal clothing.
- Do not swallow the study cream. If you do, call your doctor.
- Do not use the study cream if you are allergic to pimecrolimus or any of the ingredients in cream.
- Avoid using the study cream on skin areas that have cancers or pre-cancers.
- Call your doctor if your symptoms get worse.

Before using the study cream, tell your doctor about all of your medical conditions, including if you:

- have a skin disease called Netherton's syndrome (a rare inherited condition)
- have any infection on your skin including chicken pox or herpes
- have been told you have a weakened immune system
- are pregnant or plan to become pregnant. It is not known if the study cream will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the study cream passes into your breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. In addition, please avoid eating grapefruit or drinking grapefruit juice while using the study medication as it may interfere with its activity. Tell your doctor about all the skin medicines and products you use.

- Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
- Do not freeze the study cream.
- Keep the study cream out of the reach of children.

Please return for study visits at the doctor's office as follows:
Visit 2 on _____at _____ am
Visit 3 on _____at _____ am
Visit 4 on _____ at _____am
Please return with your study diary and any tubes of study cream that you may have.

12.7 Appendix VI: Revision History Dated 14Oct2016

Section	Revisions
Title Pages	CRO and Sponsor contact information was updated
Title Pages and Protocol Approval Signature Pages	Administrative Structure section was deleted and will be replaced with the Contact List to be distributed separately
Investigator Protocol Agreement	Investigator Protocol Agreement was updated to include mention of **training and experience** for delegation consideration as well as **Ethics Committee** as one of the bodies that may have access to the study information
Study Synopsis and **Section 3.1**	Screening criteria clarified: • using Cetaphil for **minimum** of 7 days **continuously** • as well as having affected area of AD involvement at least 5% body surface area (BSA), removing requirement of having this criteria be met at baseline
Study Synopsis and **Section 3.1**	Inclusion/Exclusion criteria was updated to include specific recommendation relating to the birth control
Study Synopsis and **Section 3.1**	Screening Period was extended to up to **14** days
Section 3.1	Clarified that if one is already using bland emollient (e.g Cetalphil® Lotion) continuously for 7 days, there is no need to be dispensed study bland emollient. In such case, procedures of Visit 1 (V1) and Visit 2 (V2) can be combined in one visit, if desired.
Section 3.1.2 and Instructions to Patients	Caregivers who are pregnant, breastfeeding or may become pregnant should consult their physicians and follow their recommendations relating to the potential exposure to Pimecrolimus 1% Cream.

Section	Revisions
Section 3.2	Clarified screening period/window as 0-14 days
Section 4.4.3	Added “assent” to section 4.4.3
Section 6.4	Clarified immunosuppressive drugs criteria.
Section 9.2.1	Clarified “safety” population instead of ITT
Patient Instructions	Clarified that prolonged baths (longer than 5 minutes) as well as grapefruit and grapefruit juice should be avoided while on the study.

12.8 Appendix VII: US Reference Listed Drug Package Insert

ELIDEL- pimecrolimus cream
Valeant Pharmaceuticals North America LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELIDEL® safely and effectively. See full prescribing information for ELIDEL®.

ELIDEL® (pimecrolimus) Cream, 1% for topical use
Initial U.S. Approval: 2001

WARNING: LONG-TERM SAFETY OF TOPICAL CALCINEURIN INHIBITORS HAS NOT BEEN ESTABLISHED

See full prescribing information for complete boxed warning.

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream, 1%. (5.1)
Therefore:

- **Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis. (2, 5.1)**
- **ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age. (1, 5.1, 8.4)**

INDICATIONS AND USAGE

ELIDEL Cream, 1% is a calcineurin inhibitor immunosuppressant indicated as *second-line therapy* for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. (1)

DOSAGE AND ADMINISTRATION

- Apply a thin layer of ELIDEL Cream, 1% to the affected skin twice daily. (2)
- If signs and symptoms persist beyond 6 weeks, patients should be re-examined. (2)
- Continuous long-term use of ELIDEL Cream, 1% should be avoided. (2)
- Avoid use with occlusive dressings. (2)

DOSAGE FORMS AND STRENGTHS

Cream, 1%. (3)

CONTRAINDICATIONS

ELIDEL® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream. (4, 6.2)

WARNINGS AND PRECAUTIONS

- Should not be used in immunocompromised adults and children, including patients on systemic immunosuppressive medications. (5.1)
- Avoid treatment on malignant or pre-malignant skin conditions, as these can present as dermatitis. (5.2)
- Should not be used in patients with Netherton's Syndrome or skin diseases with a potential for increased systemic absorption. (5.2)

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥1%) were application site burning, headache, nasopharyngitis, cough, influenza, pyrexia and viral infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: LONG-TERM SAFETY OF TOPICAL CALCINEURIN INHIBITORS HAS NOT BEEN ESTABLISHED
1 INDICATION AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Immunosuppression
5.2 Application to Malignant or Pre-malignant Skin Conditions
5.3 Bacterial and Viral Skin Infections
5.4 Patients with Lymphadenopathy
5.5 Sun Exposure
5.6 Immunocompromised Patients
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6.1 Clinical Trials Experience
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8 USE IN SPECIFIC POPULATIONS
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11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LONG-TERM SAFETY OF TOPICAL CALCINEURIN INHIBITORS HAS NOT BEEN ESTABLISHED

Although a causal relationship has not been established, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream, 1% [see *Warnings and Precautions (5.1)*].
Therefore:

- **Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis [see *Dosage and Administration (2), Warnings and Precautions (5.1)*].**
- **ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age [see *Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**

1 INDICATION AND USAGE

ELIDEL® (pimecrolimus) Cream, 1% is indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.

ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age [see *Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].

2 DOSAGE AND ADMINISTRATION

Apply a thin layer of ELIDEL (pimecrolimus) Cream, 1% to the affected skin twice daily. The patient should stop using ELIDEL Cream, 1% when signs and symptoms (e.g., itch, rash and redness) resolve and should be instructed on what actions to take if symptoms recur.

If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis of atopic dermatitis.

Continuous long-term use of ELIDEL Cream, 1% should be avoided, and application should be limited to areas of involvement with atopic dermatitis [see *Warnings and Precautions (5.1)*].

The safety of ELIDEL Cream, 1% under occlusion, which may promote systemic exposure, has not been evaluated. Avoid use of ELIDEL Cream, 1% with occlusive dressings.

3 DOSAGE FORMS AND STRENGTHS

Cream, 1%.

Each gram of ELIDEL Cream, 1% contains 10 mg of pimecrolimus in a whitish cream base.

4 CONTRAINDICATIONS

ELIDEL® (pimecrolimus) Cream, 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Immunosuppression

Prolonged systemic use of calcineurin inhibitors for sustained immunosuppression in animal studies and transplant patients following systemic administration has been associated with an increased risk of infections, lymphomas, and skin malignancies. These risks are associated with the intensity and duration of immunosuppression.

Based on this information and the mechanism of action, there is a concern about a potential risk with the use of topical calcineurin inhibitors, including ELIDEL Cream, 1%. While a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with topical calcineurin inhibitors, including ELIDEL Cream, 1%. Therefore:

- Continuous long-term use of topical calcineurin inhibitors, including ELIDEL Cream, 1%, in any age group should be avoided, and application limited to areas of involvement with atopic dermatitis
- ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age
- ELIDEL Cream, 1% should not be used in immunocompromised adults and children, including patients on systemic immunosuppressive medications.
- If signs and symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider and their diagnosis be confirmed.

- The safety of ELIDEL Cream, 1% has not been established beyond one year of non-continuous use.

5.2 Application to Malignant or Pre-malignant Skin Conditions

The use of ELIDEL Cream, 1% should be avoided on malignant or pre-malignant skin conditions. Malignant or pre-malignant skin conditions, such as cutaneous T-cell lymphoma (CTCL), can present as dermatitis.

ELIDEL Cream, 1% should not be used in patients with Netherton's Syndrome or other skin diseases where there is the potential for increased systemic absorption of pimecrolimus. The safety of ELIDEL Cream, 1% has not been established in patients with generalized erythroderma.

The use of ELIDEL Cream, 1% may cause local symptoms such as skin burning (burning sensation, stinging, soreness) or pruritus. Localized symptoms are most common during the first few days of ELIDEL Cream, 1% application and typically improve as the lesions of atopic dermatitis resolve [see *Adverse Reactions (6.1)*].

5.3 Bacterial and Viral Skin Infections

Before commencing treatment with ELIDEL Cream, 1%, bacterial or viral infections at treatment sites should be resolved. Trials have not evaluated the safety and efficacy of ELIDEL Cream, 1% in the treatment of clinically infected atopic dermatitis.

While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with ELIDEL Cream, 1% may be independently associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum.

In clinical trials, 15/1,544 (1%) cases of skin papilloma (warts) were observed in subjects using ELIDEL Cream, 1%. The youngest subject was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of ELIDEL Cream, 1% should be considered until complete resolution of the warts is achieved.

5.4 Patients with Lymphadenopathy

In clinical trials, 14/1,544 (0.9%) cases of lymphadenopathy were reported while using ELIDEL Cream, 1%. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive ELIDEL Cream, 1% and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, ELIDEL Cream, 1% should be discontinued. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves.

5.5 Sun Exposure

During the course of treatment, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure, even while ELIDEL Cream, 1% is not on the skin. The potential effects of ELIDEL Cream, 1% on skin response to ultraviolet damage are not known.

5.6 Immunocompromised Patients

The safety and efficacy of ELIDEL Cream, 1% in immunocompromised patients have not been studied.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed

in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

No phototoxicity and no photoallergenicity were detected in clinical trials with 24 and 33 normal volunteers, respectively. In human dermal safety trials, ELIDEL (pimecrolimus) Cream, 1% did not induce contact sensitization or cumulative irritation.

In a one-year safety trial in pediatric subjects age 2-17 years old involving sequential use of ELIDEL Cream, 1% and a topical corticosteroid, 43% of ELIDEL Cream, 1% treated subjects and 68% of vehicle-treated subjects used corticosteroids during the trial. Corticosteroids were used for more than 7 days by 34% of ELIDEL Cream, 1% treated subjects and 54% of vehicle-treated subjects. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the subjects that had used ELIDEL Cream, 1% and topical corticosteroid sequentially as compared to ELIDEL Cream, 1% alone.

In 3 randomized, double-blind vehicle-controlled pediatric trials and one active-controlled adult trial, 843 and 328 subjects respectively, were treated with ELIDEL Cream, 1%. In these clinical trials, 48 (4%) of the 1,171 ELIDEL treated subjects and 13 (3%) of 408 vehicle-treated subjects discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8%-26% of subjects treated with ELIDEL Cream, 1%.

Table 1 depicts the incidence of adverse events pooled across the 2 identically designed 6-week trials with their open label extensions and the 1-year safety trial for pediatric subjects ages 2-17. Data from the adult active-controlled trial is also included in Table 1. Adverse events are listed regardless of relationship to trial drug.

Table 1: Treatment Emergent Adverse Events (≥1%) in Elidel® Treatment Groups

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Elidel® Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel® Cream (N=335) N (%)	Elidel® Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel® Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)
Infections and Infestations						
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)

Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	<1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General Disorders and Administration Site Conditions						
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	<1%	<1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	<1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)

Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal Disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	15 (5.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	21 (7.7%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	<1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	<1%	<1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (0.4%)	<1%	3 (0.9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and Poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1%	1 (1.3%)	0
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)	<1%	<1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	<1%	0	6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.9%)	2 (2.7%)	0
Nervous System Disorders						
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

* Ages 2-17 years

Two cases of septic arthritis have been reported in infants less than one year of age in clinical trials conducted with ELIDEL Cream, 1% (n = 2,443). Causality has not been established.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ELIDEL Cream, 1%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: Anaphylactic reactions, ocular irritation after application of the cream to the eye lids or near the eyes, angioneurotic edema, facial edema, skin flushing associated with alcohol use, skin discoloration.

Hematology/Oncology: Lymphomas, basal cell carcinoma, malignant melanoma, squamous cell carcinoma.

7 DRUG INTERACTIONS

Potential interactions between ELIDEL Cream, 1% and other drugs, including immunizations, have not been systematically evaluated. Due to low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with ELIDEL Cream, 1% in pregnant women. Therefore, ELIDEL Cream, 1% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In dermal embryofetal developmental studies, no maternal or fetal toxicity was observed up to the highest practicable doses tested, 10 mg/kg/day (1% pimecrolimus cream) in rats (0.14× MRHD based on body surface area) and 10 mg/kg/day (1% pimecrolimus cream) in rabbits (0.65× MRHD based on AUC comparisons). The 1% pimecrolimus cream was administered topically for 6 hours/day during the period of organogenesis in rats and rabbits (gestational days 6-21 in rats and gestational days 6-20 in rabbits).

A second dermal embryofetal development study was conducted in rats using pimecrolimus cream applied dermally to pregnant rats (1 g cream/kg body weight of 0.2%, 0.6% and 1.0% pimecrolimus cream) from gestation day 6 to 17 at doses of 2, 6, and 10 mg/kg/day with daily exposure of approximately 22 hours. No maternal, reproductive, or embryo-fetal toxicity attributable to pimecrolimus was noted at 10 mg/kg/day (0.66× MRHD based on AUC comparisons), the highest dose evaluated in this study. No teratogenicity was noted in this study at any dose.

A combined oral fertility and embryofetal developmental study was conducted in rats and an oral embryofetal developmental study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (2 weeks prior to mating until gestational day 16 in rats, gestational days 6-18 in rabbits) up to dose levels of 45 mg/kg/day in rats and 20 mg/kg/day in rabbits. In the absence of maternal toxicity, indicators of embryofetal toxicity (post-implantation loss and reduction in litter size) were noted at 45 mg/kg/day (38× MRHD based on AUC comparisons) in the oral fertility and embryofetal developmental study conducted in rats. No malformations in the fetuses were noted at 45 mg/kg/day (38× MRHD based on AUC comparisons) in this study. No maternal toxicity, embryotoxicity or teratogenicity were noted in the oral rabbit embryofetal developmental toxicity study at 20 mg/kg/day (3.9× MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral embryofetal development study was conducted in rats. Pimecrolimus was administered during the period of organogenesis (gestational days 6 – 17) at doses of 2, 10 and 45 mg/kg/day. Maternal toxicity, embryolethality and fetotoxicity were noted at 45 mg/kg/day (271× MRHD based on AUC comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryolethality or fetotoxicity were noted at 10 mg/kg/day (16× MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

A second oral embryofetal development study was conducted in rabbits. Pimecrolimus was administered during the period of organogenesis (gestational days 7 – 20) at doses of 2, 6 and 20 mg/kg/day. Maternal toxicity, embryotoxicity and fetotoxicity were noted at 20 mg/kg/day (12× MRHD based on AUC

comparisons). A slight increase in skeletal variations that were indicative of delayed skeletal ossification was also noted at this dose. No maternal toxicity, embryotoxicity or fetotoxicity were noted at 6 mg/kg/day (5× MRHD based on AUC comparisons). No teratogenicity was noted in this study at any dose.

An oral peri- and post-natal developmental study was conducted in rats. Pimecrolimus was administered from gestational day 6 through lactational day 21 up to a dose level of 40 mg/kg/day. Only 2 of 22 females delivered live pups at the highest dose of 40 mg/kg/day. Postnatal survival, development of the F1 generation, their subsequent maturation and fertility were not affected at 10 mg/kg/day (12× MRHD based on AUC comparisons), the highest dose evaluated in this study.

Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

ELIDEL Cream, 1% is not indicated for use in children less than 2 years of age.

The long-term safety and effects of ELIDEL Cream, 1% on the developing immune system are unknown.

Three Phase 3 pediatric trials were conducted involving 1,114 subjects 2-17 years of age. Two trials were 6-week randomized vehicle-controlled trials with a 20-week open-label phase and one was a vehicle-controlled (up to 1 year) safety trial with the option for sequential topical corticosteroid use. Of these subjects 542 (49%) were 2-6 years of age. In the short-term trials, 11% of ELIDEL subjects did not complete these trials and 1.5% of ELIDEL subjects discontinued due to adverse events. In the one-year trial, 32% of ELIDEL subjects did not complete this trial and 3% of ELIDEL subjects discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect.

The most common local adverse event in the short-term trials of ELIDEL Cream, 1% in pediatric subjects ages 2-17 was application site burning (10% vs. 13% vehicle); the incidence in the long-term trial was 9% ELIDEL vs. 7% vehicle [see *Adverse Reactions (6.1)*]. Adverse events that were more frequent (>5%) in subjects treated with ELIDEL Cream, 1% compared to vehicle were headache (14% vs. 9%) in the short-term trial. Nasopharyngitis (26% vs. 21%), influenza (13% vs. 4%), pharyngitis (8% vs. 3%), viral infection (7% vs. 1%), pyrexia (13% vs. 5%), cough (16% vs. 11%), and headache (25% vs. 16%) were increased over vehicle in the 1-year safety trial [see *Adverse Reactions (6.1)*]. In 843 subjects ages 2-17 years treated with ELIDEL Cream, 1%, 9 (0.8%) developed eczema herpeticum (5 on ELIDEL Cream, 1% alone and 4 on ELIDEL Cream, 1% used in sequence with corticosteroids). In 211 subjects on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity.

Two Phase 3 trials were conducted involving 436 infants age 3 months-23 months. One 6-week randomized vehicle-controlled trial with a 20-week open-label phase and one safety trial, up to one year, were conducted. In the 6-week trial, 11% of ELIDEL and 48% of vehicle subjects did not complete this trial; no subject in either group discontinued due to adverse events. Infants on ELIDEL Cream, 1% had an increased incidence of some adverse events compared to vehicle. In the 6-week vehicle-controlled trial these adverse events included pyrexia (32% vs. 13% vehicle), URI (24% vs. 14%), nasopharyngitis (15% vs. 8%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%), and diarrhea (8% vs. 0%). In the open-label phase of the trial, for infants who switched to ELIDEL Cream, 1% from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those subjects who remained on ELIDEL Cream, 1%. In the 6 month safety data, 16% of ELIDEL and 35% of vehicle subjects discontinued early and 1.5% of ELIDEL and 0% of vehicle subjects discontinued due to adverse events. Infants on ELIDEL Cream, 1% had a greater incidence of some

adverse events as compared to vehicle. These included pyrexia (30% vs. 20%), URI (21% vs. 17%), cough (15% vs. 9%), hypersensitivity (8% vs. 2%), teething (27% vs. 22%), vomiting (9% vs. 4%), rhinitis (13% vs. 9%), viral rash (4% vs. 0%), rhinorrhea (4% vs. 0%), and wheezing (4% vs. 0%).

The systemic exposure to pimecrolimus from ELIDEL (pimecrolimus) Cream, 1% was investigated in 28 pediatric subjects with atopic dermatitis (20%-80% BSA involvement) between the ages of 8 months-14 yrs. Following twice daily application for three weeks, blood concentrations of pimecrolimus were <2 ng/mL with 60% (96/161) of the blood samples having blood concentration below the limit of quantification (0.5 ng/mL). However, more children (23 children out of the total 28 children investigated) had at least one detectable blood level as compared to the adults (12 adults out of the total 52 adults investigated) over a 3-week treatment period. Due to the erratic nature of the blood levels observed, no correlation could be made between amount of cream, degree of BSA involvement, and blood concentrations. In general, the blood concentrations measured in adult atopic dermatitis subjects were comparable to those seen in the pediatric population.

In a second group of 30 pediatric subjects aged 3-23 months with 10%-92% BSA involvement, following twice daily application for three weeks, blood concentrations of pimecrolimus were <2.6 ng/mL with 65% (75/116) of the blood samples having blood concentration below 0.5 ng/mL, and 27% (31/116) below the limit of quantification (0.1 ng/mL) for these trials.

Overall, a higher proportion of detectable blood levels was seen in the pediatric subject population as compared to adult population. This increase in the absolute number of positive blood levels may be due to the larger surface area to body mass ratio seen in these younger subjects. In addition, a higher incidence of upper respiratory symptoms/infections was also seen relative to the older age group in the PK trials. At this time, a causal relationship between these findings and ELIDEL use cannot be ruled out.

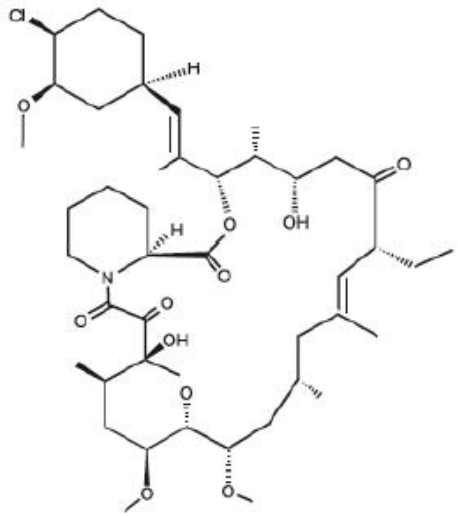
8.5 Geriatric Use

Nine (9) subjects ≥65 years old received ELIDEL Cream, 1% in Phase 3 trials. Clinical trials of ELIDEL Cream, 1% did not include sufficient numbers of subjects aged 65 and over to assess efficacy and safety.

11 DESCRIPTION

ELIDEL® (pimecrolimus) Cream, 1%, for topical use, contains the compound pimecrolimus, the immunosuppressant 33-epi-chloro-derivative of the macrolactam ascomycin.

Chemically, pimecrolimus is (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-ethyl-1, 14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-aza-tricyclo[22.3.1.0 ^{4,9}]octacos-18-ene-2,3,10,16-tetraone. The compound has the empirical formula $C_{43}H_{68}ClNO_{11}$ and the molecular weight of 810.47. The structural formula is



Pimecrolimus is a white to off-white fine crystalline powder. It is soluble in methanol and ethanol and insoluble in water.

Each gram of ELIDEL Cream, 1% contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid anhydrous, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimecrolimus in atopic dermatitis is not known. While the following have been observed, the clinical significance of these observations in atopic dermatitis is not known. It has been demonstrated that pimecrolimus binds with high affinity to macrophilin-12 (FKBP-12) and inhibits the calcium-dependent phosphatase, calcineurin. As a consequence, it inhibits T cell activation by blocking the transcription of early cytokines. In particular, pimecrolimus inhibits at nanomolar concentrations Interleukin-2 and interferon gamma (Th1-type) and Interleukin-4 and Interleukin-10 (Th2-type) cytokine synthesis in human T-cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.

12.3 Pharmacokinetics

Absorption

In adult subjects (n=52) being treated for atopic dermatitis [13%-62% Body Surface Area (BSA) involvement] for periods up to a year, a maximum pimecrolimus concentration of 1.4 ng/mL was observed among those subjects with detectable blood levels. In the majority of samples in adult (91%; 1,244/1,362) subjects, blood concentrations of pimecrolimus were below 0.5 ng/mL. Data on blood levels of pimecrolimus measured in pediatric subjects are described in Use in Specific Populations (8.4).

Distribution

Laboratory in vitro plasma protein binding studies using equilibrium gel filtration have shown that 99.5% of pimecrolimus in plasma is bound to proteins over the pimecrolimus concentration range of 2-100 ng/mL tested. The major fraction of pimecrolimus in plasma appears to be bound to various

lipoproteins. As with other topical calcineurin inhibitors, it is not known whether pimecrolimus is absorbed into cutaneous lymphatic vessels or in regional lymph nodes.

Metabolism

Following the administration of a single oral radiolabeled dose of pimecrolimus numerous circulating O-demethylation metabolites were seen. Studies with human liver microsomes indicate that pimecrolimus is metabolized in vitro by the CYP3A sub-family of metabolizing enzymes. No evidence of skin mediated drug metabolism was identified in vivo using the minipig or in vitro using stripped human skin.

Elimination

Based on the results of the aforementioned radiolabeled study, following a single oral dose of pimecrolimus ~81% of the administered radioactivity was recovered, primarily in the feces (78.4%) as metabolites. Less than 1% of the radioactivity found in the feces was due to unchanged pimecrolimus.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat dermal carcinogenicity study using ELIDEL Cream, 1%, a statistically significant increase in the incidence of follicular cell adenoma of the thyroid was noted in low, mid and high dose male animals compared to vehicle and saline control male animals. Follicular cell adenoma of the thyroid was noted in the dermal rat carcinogenicity study at the lowest dose of 2 mg/kg/day [0.2% pimecrolimus cream; 1.5× the Maximum Recommended Human Dose (MRHD) based on AUC comparisons]. No increase in the incidence of follicular cell adenoma of the thyroid was noted in the oral carcinogenicity study in male rats up to 10 mg/kg/day (66× MRHD based on AUC comparisons). However, oral studies may not reflect continuous exposure or the same metabolic profile as by the dermal route. In a mouse dermal carcinogenicity study using pimecrolimus in an ethanolic solution, no increase in incidence of neoplasms was observed in the skin or other organs up to the highest dose of 4 mg/kg/day (0.32% pimecrolimus in ethanol) 27× MRHD based on AUC comparisons. However, lymphoproliferative changes (including lymphoma) were noted in a 13 week repeat dose dermal toxicity study conducted in mice using pimecrolimus in an ethanolic solution at a dose of 25 mg/kg/day (47× MRHD based on AUC comparisons). No lymphoproliferative changes were noted in this study at a dose of 10 mg/kg/day (17× MRHD based on AUC comparison). However, the latency time to lymphoma formation was shortened to 8 weeks after dermal administration of pimecrolimus dissolved in ethanol at a dose of 100 mg/kg/day (179-217× MRHD based on AUC comparisons).

In a mouse oral (gavage) carcinogenicity study, a statistically significant increase in the incidence of lymphoma was noted in high dose male and female animals compared to vehicle control male and female animals. Lymphomas were noted in the oral mouse carcinogenicity study at a dose of 45 mg/kg/day (258-340× MRHD based on AUC comparisons). No drug-related tumors were noted in the mouse oral carcinogenicity study at a dose of 15 mg/kg/day (60-133× MRHD based on AUC comparisons).

In an oral (gavage) rat carcinogenicity study, a statistically significant increase in the incidence of benign thymoma was noted in 10 mg/kg/day pimecrolimus treated male and female animals compared to vehicle control treated male and female animals. In addition, a significant increase in the incidence of benign thymoma was noted in another oral (gavage) rat carcinogenicity study in 5 mg/kg/day pimecrolimus treated male animals compared to vehicle control treated male animals. No drug-related tumors were noted in the rat oral carcinogenicity study at a dose of 1 mg/kg/day male animals (1.1× MRHD based on AUC comparisons) and at a dose of 5 mg/kg/day for female animals (21× MRHD based on AUC comparisons).

In a 52-week dermal photo-carcinogenicity study, the median time to onset of skin tumor formation was decreased in hairless mice following chronic topical dosing with concurrent exposure to UV radiation (40 weeks of treatment followed by 12 weeks of observation) with the ELIDEL Cream, 1% vehicle

alone. No additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient, pimecrolimus, to the vehicle cream.

A 39-week oral monkey toxicology study was conducted with pimecrolimus doses of 15, 45 and 120 mg/kg/day. A dose dependent increase in expression of immunosuppressive-related lymphoproliferative disorder (IRLD) associated with lymphocryptovirus (a monkey strain of virus related to human Epstein Barr virus) was observed. IRLD in monkeys mirrors what has been noted in human transplant patients after chronic systemic immunosuppressive therapy, post transplantation lymphoproliferative disease (PTLD), after treatment with chronic systemic immunosuppressive therapy. Both IRLD and PTLD can progress to lymphoma, which is dependent on the dose and duration of systemic immunosuppressive therapy. A dose dependent increase in opportunistic infections (a signal of systemic immunosuppression) was also noted in this monkey study. A no observed adverse effect level (NOAEL) for IRLD and opportunistic infections was not established in this study. IRLD occurred at the lowest dose of 15 mg/kg/day for 39 weeks [31× the Maximum Recommended Human Dose (MRHD) of ELIDEL Cream, 1% based on AUC comparisons] in this study. A partial recovery from IRLD was noted upon cessation of dosing in this study.

A battery of in vitro genotoxicity tests, including Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an in vivo mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug.

An oral fertility and embryofetal developmental study in rats revealed estrus cycle disturbances, post-implantation loss and reduction in litter size at the 45 mg/kg/day dose (38× MRHD based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (12× MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23× MRHD based on AUC comparisons), which was the highest dose tested in this study.

A second oral fertility and embryofetal developmental study in rats revealed reduced testicular and epididymal weights, reduced testicular sperm counts and motile sperm for males and estrus cycle disturbances, decreased corpora lutea, decreased implantations and viable fetuses for females at 45 mg/kg/day dose (123× MRHD for males and 192× MRHD for females based on AUC comparisons). No effect on fertility in female rats was noted at 10 mg/kg/day (5× MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 2 mg/kg/day (0.7× MRHD based on AUC comparisons).

14 CLINICAL STUDIES

Three randomized, double-blind, vehicle-controlled, multi-center, Phase 3 trials were conducted in 589 pediatric subjects ages 3 months-17 years old to evaluate ELIDEL (pimecrolimus) Cream, 1% for the treatment of mild to moderate atopic dermatitis. Two of the three trials support the use of ELIDEL Cream, 1% in subjects 2 years and older with mild to moderate atopic dermatitis [see *Warnings and Precautions (5.1)*]. Three other trials in 1,619 pediatric and adult subjects provided additional data regarding the safety of ELIDEL Cream, 1% in the treatment of atopic dermatitis. Two of these other trials were vehicle-controlled with optional sequential use of a medium potency topical corticosteroid in pediatric subjects and one trial was an active comparator trial in adult subjects with atopic dermatitis [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*].

Two identical 6-week, randomized, vehicle-controlled, multi-center, Phase 3 trials were conducted to evaluate ELIDEL Cream, 1% for the treatment of mild to moderate atopic dermatitis. A total of 403 pediatric subjects 2-17 years old were included in the trials. The male/female ratio was approximately 50% and 29% of the subjects were African American. At trial entry, 59% of subjects had moderate disease and the mean body surface area (BSA) affected was 26%. About 75% of subjects had atopic dermatitis affecting the face and/or neck region. In these trials, subjects applied either ELIDEL Cream, 1% or vehicle cream twice daily to 5% to 96% of their BSA for up to 6 weeks. At endpoint, based on the physician's global evaluation of clinical response, 35% of subjects treated with ELIDEL Cream, 1% were clear or almost clear of signs of atopic dermatitis compared to only 18% of vehicle-treated subjects. More ELIDEL subjects (57%) had mild or no pruritus at 6 weeks compared to vehicle subjects

(34%). The improvement in pruritus occurred in conjunction with the improvement of the subjects' atopic dermatitis.

In these two 6-week studies of ELIDEL, the combined efficacy results at endpoint are presented in Table 2 as follows:

Table 2: Combined Efficacy Results at Endpoint for Two 6-week Trials of ELIDEL Cream

	% Subjects	
	Elidel® (N= 267)	**Vehicle (N= 136)**
Global Assessment		
Clear	28 (10%)	5 (4%)
Clear or Almost Clear	93 (35%)	25 (18%)
Clear to Mild Disease	180 (67%)	55 (40%)

In the two pediatric trials that independently support the use of ELIDEL Cream, 1% in mild to moderate atopic dermatitis, a significant treatment effect was seen by day 15. Of the key signs of atopic dermatitis, erythema, infiltration/papulation, lichenification, and excoriations were reduced at day 8 when compared to vehicle.

Figure 1 depicts the time course of improvement in the percent body surface area affected as a result of treatment with ELIDEL Cream, 1% in 2-17 year olds.

Figure 1

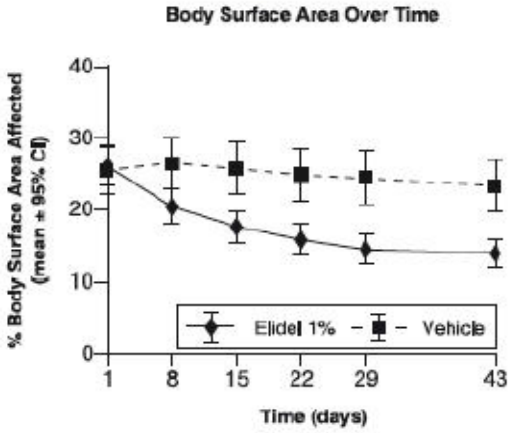
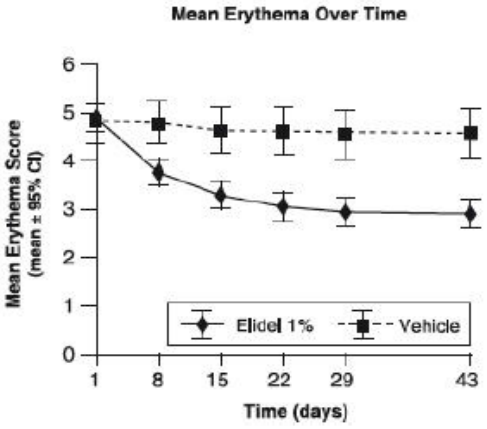


Figure 2 shows the time course of improvement in erythema as a result of treatment with ELIDEL Cream, 1% in 2-17 year olds.

Figure 2



16 HOW SUPPLIED/STORAGE AND HANDLING

ELIDEL (pimecrolimus) Cream, 1% is a whitish cream available in tubes of 30 grams, 60 grams, and 100 grams.

30 gram tube	NDC 0187-5100-01
60 gram tube	NDC 0187-5101-02
100 gram tube	NDC 0187-5102-03

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [USP Controlled Room Temperature]. Do not freeze.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients using ELIDEL Cream, 1% should receive the following information and instructions:

- **ELIDEL Cream, 1% may cause serious side effects.** It is not known if ELIDEL Cream, 1% is safe to use for a long period of time. A very small number of people who have used ELIDEL Cream, 1% have had cancer (for example, skin or lymphoma). However, a link with ELIDEL Cream, 1% use has not been shown. Because of this concern:
- A patient should not use ELIDEL Cream, 1% continuously for a long time.
- ELIDEL Cream, 1% should be used only on areas of skin that have eczema.
- ELIDEL Cream, 1% is not for use on a child under 2 years old.
- A patient should not use sun lamps, tanning beds, or get treatment with ultraviolet light therapy during treatment with ELIDEL Cream, 1%.
- A patient should limit sun exposure during treatment with ELIDEL Cream, 1% even when the medicine is not on the skin. If a patient needs to be outdoors after applying ELIDEL Cream, 1%, the patient should wear loose fitting clothing that protects the treated area from the sun. The physician should advise the patient about other types of protection from the sun.
- A patient should not cover the skin being treated with bandages, dressings or wraps. A patient can wear normal clothing.
- ELIDEL Cream, 1% is for use on the skin only. Do not get ELIDEL Cream, 1% in your eyes, nose, mouth, vagina, or rectum (mucous membranes). If you get ELIDEL Cream, 1% in any of these areas, burning or irritation can happen. Wipe off any ELIDEL Cream, 1% from the affected area and then rinse the area well with cold water. ELIDEL Cream, 1% is for external use only.

- A patient should use ELIDEL Cream, 1% for short periods, and if needed, treatment may be repeated with breaks in between.
- Wash hands before using ELIDEL Cream, 1%. When applying ELIDEL Cream, 1% after a bath or shower, the skin should be dry.
- Apply a thin layer of ELIDEL Cream, 1% only to the affected skin areas, twice a day, as directed by the physician.
- Use the smallest amount of ELIDEL Cream, 1% needed to control the signs and symptoms of eczema.
- A patient should not bathe, shower or swim right after applying ELIDEL Cream, 1%. This could wash off the cream.
- A patient can use moisturizers with ELIDEL Cream, 1%. They should be sure to check with the physician first about the products that are right for them. Because the skin of patients with eczema can be very dry, it is important they keep up good skin care practices. If a patient uses moisturizers, he or she should apply them after ELIDEL Cream, 1%.

Manufactured by:
Valeant Pharmaceuticals International Inc.
Laval, Quebec H7L 4A8, Canada
or
Novartis Pharma Produktions GmbH
Wehr, Germany

For:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Made in Canada or Germany

U.S. Patents 5,912,238; 6,352,998; and 6,423,722

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Valeant Pharmaceuticals International Inc. PI:
Rev. 08/2014
9413902

Novartis Pharma Produktions GmbH PI:
Rev. 03/2014
9386701

MEDICATION GUIDE

ELIDEL® (EL´-ee-del)
(pimecrolimus)
Cream, 1%

Important: ELIDEL Cream, 1% is for use on the skin only (topical). Do not get ELIDEL Cream, 1% in your eyes, nose, mouth, vagina, or rectum.

What is the most important information I should know about ELIDEL Cream, 1%?

It is not known if ELIDEL Cream, 1% is safe to use for a long period of time. A very small number of people who have used ELIDEL Cream, 1% have developed cancer (for example, skin cancer or

lymphoma). But a link that ELIDEL Cream, 1% use caused these cancers has not been shown. Because of this concern:

- Do not use ELIDEL Cream, 1% continuously for a long time.
- Use ELIDEL Cream, 1% only on areas of your skin that have eczema.
- Do not use ELIDEL Cream, 1% on a child under 2 years of age.

What is ELIDEL Cream, 1%?

ELIDEL Cream, 1% is a prescription medicine used on the skin (topical) to treat mild to moderate eczema (atopic dermatitis). ELIDEL Cream, 1% is for adults and children age 2 years and older who do not have a weakened immune system. ELIDEL Cream, 1% is used on the skin for short periods, and if needed, treatment may be repeated with breaks in between. ELIDEL Cream, 1% is for use after other prescription medicines have not worked for you or if your doctor recommends that other prescription medicines should not be used.

It is not known if ELIDEL Cream, 1% is safe and effective in people who have a weakened immune system.

ELIDEL Cream, 1% is not for use in children under 2 years of age

Who should not use ELIDEL Cream, 1%?

Do not use ELIDEL Cream, 1% if you are allergic to pimecrolimus or any of the ingredients in ELIDEL Cream, 1%. See the end of this Medication Guide for a complete list of ingredients in ELIDEL Cream, 1%.

What should I tell my doctor before using ELIDEL Cream, 1%?

Before using ELIDEL Cream, 1%, tell your doctor about all of your medical conditions, including if you:

- have a skin disease called Netherton's syndrome (a rare inherited condition)
- have any infection on your skin including chicken pox or herpes
- have been told you have a weakened immune system
- are pregnant or plan to become pregnant. It is not known if ELIDEL Cream, 1% will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ELIDEL Cream, 1% passes into your breast milk. You and your doctor should decide if you will use ELIDEL Cream, 1% or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tell your doctor about all the skin medicines and products you use.

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

How should I use ELIDEL Cream, 1%?

- Use ELIDEL Cream, 1% exactly as your doctor tells you to use it.
- Stop ELIDEL Cream, 1% when the signs and symptoms of eczema, such as itching, rash, and redness go away, or as directed by your doctor.
- Wash your hands before using ELIDEL Cream, 1%. If you apply ELIDEL Cream, 1% after a bath or shower, make sure your skin is dry.
- Apply a thin layer of ELIDEL Cream, 1% only to the affected skin areas, two times each day, as directed by your doctor.
- Use the smallest amount of ELIDEL Cream, 1% to help control the signs and symptoms of eczema.
- If you apply ELIDEL Cream, 1% to another person, or if you have eczema and are not treating your hands, it is important for you to wash your hands with soap and water after applying ELIDEL Cream,

1%. This should remove any cream left on your hands.
- Do not bathe, shower or swim right after applying ELIDEL Cream, 1%. This could wash off the cream.
- You can use moisturizers with ELIDEL Cream, 1%. Ask your doctor first about the products that are right for you. People with eczema can have very dry skin, so it is important to keep up good skin care practices. If you use moisturizers, apply them after ELIDEL Cream, 1%.
- **Call your doctor if your symptoms get worse with ELIDEL Cream, 1% or your symptoms do not improve after 6 weeks of treatment.**

What should I avoid while using ELIDEL Cream, 1%?
- You should not use sun lamps, tanning beds, or get treatment with ultraviolet light therapy during treatment with ELIDEL Cream, 1%.
- Limit your time in the sun during treatment with ELIDEL Cream, 1% even when the medicine is not on your skin. If you need to be outdoors after applying ELIDEL Cream, 1%, wear loose fitting clothing that protects the treated area from the sun. Ask your doctor what other types of protection from the sun you should use. It is not known how ELIDEL Cream, 1% may affect your skin with exposure to ultraviolet light.
- Do not cover the skin being treated with bandages, dressings or wraps. You can wear normal clothing.
- ELIDEL Cream, 1% is for use on the skin only. Do not get ELIDEL Cream, 1% in your eyes, nose, mouth, vagina, or rectum (mucous membranes). If you get ELIDEL Cream, 1% in any of these areas, burning or irritation can happen. Wipe off any ELIDEL Cream, 1% from the affected area and then rinse the area well with cold water.
- Do not swallow ELIDEL Cream, 1%. If you do, call your doctor.
- Avoid using ELIDEL Cream, 1% on skin areas that have cancers or pre-cancers.

What are the possible side effects of ELIDEL Cream, 1%?

ELIDEL Cream, 1% may cause serious side effects.
- See "**What is the most important information I should know about ELIDEL Cream, 1%?**"
- The most common side effect at the skin application site is burning or a feeling of warmth. These side effects are usually mild or moderate, happen during the first few days of treatment, and usually clear up in a few days.

Other common side effects include:
- headache
- common cold or stuffy nose, sore throat
- cough
- flu (influenza)
- fever
- viral infection. Some people may get viral skin infections (like cold sores, chicken pox, shingles, or warts) or swollen lymph nodes (glands).

Tell your doctor if you get a skin infection or if you have any side effect (for example, swollen glands) that bothers you or that does not go away.

These are not all the possible side effects with ELIDEL Cream, 1%. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ELIDEL Cream, 1%?
- Store ELIDEL Cream, 1% at room temperature between 68° to 77°F (20° to 25°C).

- Do not freeze ELIDEL Cream, 1%.
- **Keep ELIDEL Cream, 1% and all medicines out of the reach of children.**

General information about the safe and effective use of ELIDEL Cream, 1%

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELIDEL Cream, 1% for conditions other than which it was prescribed. Do not give ELIDEL Cream, 1% to other people even if they have the same symptoms you have. It may harm them.

You can ask your doctor or pharmacist for information about ELIDEL Cream, 1% that is written for health professionals.

For more information, go to www.Elidel.com or call 1-800-321-4576.

What are the ingredients in ELIDEL Cream, 1%?

Active ingredient: pimecrolimus

Inactive ingredients: benzyl alcohol, cetyl alcohol, citric acid anhydrous, mono- and di-glycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Valeant Pharmaceuticals International Inc.
Laval, Quebec H7L 4A8, Canada
or
Novartis Pharma Produktions GmbH
Wehr, Germany

For:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Made in Canada or Germany

U.S. Patents 5,912,238; 6,352,998; and 6,423,722

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Rev. 03/2014
9386701

PRINCIPAL DISPLAY PANEL - 100 g Carton

NDC 0187-5102-03

ELIDEL®
(pimecrolimus) cream 1%

100 g

Rx only

FOR TOPICAL USE ONLY.
NOT FOR OPHTHALMIC USE.

If Elidel Cream gets in your eyes, rinse your eyes with cold water.

ATTENTION PHARMACIST:
Each patient is required to receive the enclosed Medication Guide.

VALEANT