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Web Page/Link to Prescribing/Label Information
http://www.pharma.us.novartis.com/product/pi.jsp

Generic Drug Name
Pimecrolimus 1% cream

Therapeutic Area of Trial
Atopic Dermatitis

Approved Indication
U.S. indication: 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 is not indicated for use in children less than 2 years of age.

Pimecrolimus is approved in the following countries: Albania, Argentina, Armenia, Aruba, Australia, Austria, Bahrain, Bangladesh, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Cuba, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Israel, Italy, Jamaica, Jordan, Kazakhstan, Korea, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Macedonia, Malaysia, Malta, Mexico, Morocco, New Zealand, Nicaragua, Norway, Palestine, Panama, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Serbia & Montenegro, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Tanzania, Thailand, The Netherlands, Trinidad & Tobago, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Uzbekistan, Venezuela, Yemen

Study Number
CASM981C2436

Title
A multicenter, 5-week, randomized, double-blind, placebo controlled, parallel group study exploring the effects of pimecrolimus cream 1% (twice daily application) vs. placebo control (twice daily application) on the molecular and cellular profile of adult male patients with atopic dermatitis.

Phase of Development
Phase IV

Study Start/End Dates
Study Start: 15 Apr 2004 to 23 Jun 05

Study Design/Methodology
This was a multicenter, randomized, double-blind, placebo controlled study exploring the effect of pimecrolimus cream 1% vs. placebo on the molecular and cellular profile of adult male patients with atopic dermatitis (AD). An open-label, 2-week run-in period: treatment with topical corticosteroid (TCS) for a maximum of 2 weeks for mild-to-moderate adult males with AD until near clearance (Eczema Area and Severity Index (EASI) =0 or 1 (clear or almost clear). Patients were randomized into a 3 week-double-blind phase (pimecrolimus vs. placebo). Healthy volunteers were the control/reference for the analysis of the molecular profile of the diseased *vs.* nondiseased population.

Centres

10 centers: United Kingdom = 1, Germany = 3, Austria = 1, United States = 3, France = 2.

Publication

Ongoing

Objectives

Primary: To determine the effect of pimecrolimus cream 1% *vs.* placebo on the molecular and cellular profile of post-lesional, but otherwise clinically normal AD skin.

Secondary: To identify early molecular and cellular changes in the acute phase of AD and determine the genomic signature of the disease by comparing AD patients before TCS treatment to untreated healthy volunteers.

Test Product (s), Dose(s), and Mode(s) of Administration

Pimecrolimus cream 1% was self-applied b.i.d. (twice daily) as a thin film to the affected area, when necessary.

Reference Product(s), Dose(s), and Mode(s) of Administration

Matched placebo (vehicle) cream was applied b.i.d. as a thin film to the affected area, when necessary.

Criteria for Evaluation

Efficacy*:* The primary and secondary objectives of this study were to explore the effects of pimecrolimus cream 1% on the molecular and cellular profile in skin biopsies and blood samples from patients with AD and healthy volunteers.

- Skin biopsies and blood samples were obtained after skin assessments were performed at visit 1 for healthy volunteers, and during visits 1, 2, and 3 for AD patients. Skin biopsy specimens from the target areas were obtained for molecular assessments (gene expression profiling; right side, which were not performed due to mRNA degradation of the biopsy samples), and for cellular assessment (immunohistochemical analyses; left side).

For cellular assessments, the target protein expressions were measured as "positively stained" cells and by different proteins assessed from biopsy and blood sample via immunohistochemistry. Target proteins of clinical interest included:

- pan T-cells (absolute CD3)
- T-helper cells ($CD4^+/CD3^+$)
- cytotoxic T-cells ($CD8^+/CD3^+$)
- $CD1a^+/Langerin^+$ (LC; Langerhans cells)
- inflammatory dendritic epidermal cells (IDEC; $CD1c^+/Cd11b^+$)
- dermal dendritic cells ($CD1c^+$)
- macrophages ($CD14^+/CD45^+$)
- all leukocytes ($CD45^+$)

The following clinical efficacy variables were also assessed:

- Localized EASI – a composite variable of the severity (rated 0-3) of erythema, infiltration/papulation, excoriations, and lichenification at the target sites as assessed by the investigator.
- Whole body Investigator Global Assessment (IGA) - a 6-point ordinal scale ranging from 0=clear to 5= very severe disease) to evaluate the patient's disease state at the time of the assessment.

Safety/tolerability*:* Safety assessments consisted of monitoring and recording all adverse events (AEs) and serious adverse events (SAEs) with severity and relationship to study drug, and regular

assessments of vital signs. Laboratory evaluations were not required in this short-term study.
Pharmacology:
Not applicable in this study

Statistical Methods

The primary statistical null hypothesis of no difference in the proportion of positively stained cells (cells/mm^2 for each cell type of interest) between the pimecrolimus cream 1% group and placebo (vehicle) control group at endpoint was analyzed using an analysis of covariance (ANCOVA) method. The secondary analyses for the proportion of positively stained cells between AD patients and healthy volunteers were performed using the unpaired two sample t-test. Safety assessments, including AEs, were summarized for the double-blinded phase.

Comparison of protein expression between pimecrolimus cream 1% *vs.* placebo (vehicle) treated patients during the post-lesional phase of AD, or AD patients (acute phase before TCS treatment) *vs.* healthy volunteers (untreated), were performed. Immunofluorescence findings were based on positive staining of cells within a defined field and comparison of antibody reactivity for specific leukocyte differentiation antigens amongst the treatment groups.

Study Population: Inclusion/Exclusion Criteria and Demographics

Included were males ≥ 20 years of age, with at least a 3 year history of AD. The diagnosis of AD was defined by the criteria of Hanifin and Rajka, and extrinsic forms of AD were identified with a prick-test and/or elevated IgE background. At screening, patients were required to have mild-to-moderate AD, defined as an IGA of the whole body (whole body IGA) of 2 (mild) or 3 (moderate); and a localized EASI of 1-8, and affecting bilateral arms and/or legs ≥ 10 cm^2. After treatment with TCS, patients were required to have a localized EASI score of ≤ 1 prior to entry into the double-blind treatment period.

Patients were excluded for: immunocompromised status, concurrent skin disease at the target site, active skin infections, history of rheumatic fever, prosthetic constituents, poor response to tacrolimus or pimecrolimus or a known hypersensitivity to study medications, serious reaction to anesthetics, or any other clinical condition that could interfere with study evaluations. Those treated with phototherapy, systemic corticosteroids or other systemic therapy known or suspected to have an effect on AD within 4 weeks prior to visit 1, antihistamines within 7 days prior to visit 1, or any topical therapy known or suspected to have an effect on AD during their current episode were also excluded.

Number of Subjects

Disposition	Pimecrolimus cream 1% n (%)	Placebo n (%)	Total n (%)
Total screened AD patients	-	-	79
Randomized	34	33	67
Exposed	34 (100.0)	33 (100.0)	67 (100.0)
Completed study	30 (88.2)	19 (57.6)	49 (73.1)
Discontinued study - Total	4 (11.8)	14 (42.4)	18 (26.9)
Primary reason for discontinuation			
Unsatisfactory therapeutic effect	4 (11.8)	14 (42.4)	18 (26.9)

Denominator used in the percentage calculations: patients randomized.
Total screened patients include patients who entered the run-in period and who failed screening.

Demographic and Background Characteristics (all enrolled population)

	AD patients N=74	Healthy volunteer N=12	Total N=86
Age (years) – summary statistics			
n	74	12	86
Mean ± SD	32.7 ± 10.75	32.3 ± 8.04	32.6 ± 10.38
Median	31.0	34.5	31.5
Range	19 – 67	20 – 47	19 – 67
Race			
Caucasian	51 (68.9)	11 (91.7)	62 (72.1)
Black	18 (24.3)	0 (0.0)	18 (20.9)
Oriental	1 (1.4)	0 (0.0)	1 (1.2)
Other	4 (5.4)	1 (8.3)	5 (5.8)

Demographic and Background Characteristics (safety population)

	Pimecrolimus cream 1% N=34	Placebo N=33	Total N=67

Age (years) – summary statistics				
n		34	33	67
Mean ± SD		31.0 ± 11.22	34.3 ± 9.92	32.6 ± 10.65
Median		27.0	34.0	32.0
Range		20 – 67	19 – 65	19 – 67
Race				
Caucasian		24 (70.6)	23 (69.7)	47 (70.1)
Black		9 (26.5)	7 (21.2)	16 (23.9
Oriental		0 (0.0)	0 (0.0)	0 (0.0)
Other		1 (2.9)	3 (9.1)	4 (6.0)

Disease characteristics by treatment (safety population)

			Pimecrolimus cream 1% N=34	**Placebo N=33**	**Total N=67**
Extent of disease – n (%)		Head / neck	22 (64.7)	26 (78.8)	48 (71.6)
		Trunk	24 (70.6)	25 (75.8)	49 (73.1)
		Upper limbs	33 (97.1)	33 (100.0)	66 (98.5)
		Lower limbs	31 (91.2)	27 (81.8)	58 (86.6)
		Whole body	17 (50.0)	19 (57.6)	36 (53.7)
Total localized EASI – summary statistics	Left	n	34	33	67
		Mean ± SD	5.6 ± 1.73	5.4 ± 1.56	5.5 ± 1.64
		Median	6.0	6.0	6.0
		Range	2 – 8	2 – 8	2 – 8
	Right	n	34	33	67
		Mean ± SD	5.4 ± 1.67	5.6 ± 1.50	5.5 ± 1.58
		Median	6.0	6.0	6.0
		Range	2 – 8	2 – 8	2 – 8
Whole body IGA – n (%)		Mild	16 (47.1)	12 (36.4)	28 (41.8)
		Moderate	18 (52.9)	21 (63.6)	39 (58.2)

EASI - Eczema Area Severity Index IGA - Investigator's Global Assessment

Primary Efficacy Result(s)

Descriptive analysis of number of positively stained cells for each cell type of interest between treatment groups at end of study (Per-protocol population)

Cell type and leukocyte differentiation antigen (cells/mm²)	Least squares means Estimate (95% CI)		Treatment difference	p-value
	Pimecrolimus cream 1% N=25	Placebo N=13		
Absolute CD3 (pan T cells)	161.6 (104.0, 219.2)	182.3 (103.8, 260.8)	-20.6 (-118.4, 77.1)	0.6705
$CD4^+/CD3^+$ (T-helper cells)	82.4 (50.9, 113.9)	97.4 (54.4, 140.4)	-15.0 (-68.6, 38.6)	0.5731
$CD8^+/CD3^+$ (cytotoxic T-cells)	81.2 (52.5, 110.0)	69.1 (30.0, 108.3)	12.1 (-36.6, 60.8)	0.6167
$CD1a^+/Langerin^+$ (LC)	3.7 (1.2, 6.3)	6.8 (3.3, 10.2)	-3.0 (-7.4, 1.3)	0.1626
$CD1c^+/Cd11b^+$ (IDEC)	34.5 (25.5, 43.5)	28.4 (16.2, 40.7)	6.1 (-9.1, 21.3)	0.4209
$CD1c^+$ (dermal dendritic cells)	137.6 (110.0, 165.2)	125.4 (87.7, 163.1)	12.2 (-34.8, 59.2)	0.6011
$CD14^+/CD45^+$ (macrophages)	50.7 (12.7, 88.7)	96.3 (42.5, 150.2)	-45.7 (-111.8, 20.5)	0.1693
$CD45^+$ (all leukocytes)	182.8 (106.1, 259.4)	267.4 (158.8, 376.0)	-84.6 (-217.9, 48.6)	0.2051

ANCOVA model: Number of positively stained cells = Treatment + Total localized EASI score (left) at screening + Number of positively stained cells at baseline before treatment.

LC - Langerhans cell IDEC - inflammatory dendritic epidermal cell

Clinical Efficacy Results:

Summary of total localized EASI by visit and treatment (safety population)

		Pimecrolimus cream 1% N=34		Placebo N=33	
		Left	Right	Left	Right
Visit 1 (screening)	n	34	34	33	33
	Mean ± SD	5.6 ± 1.73	5.4 ± 1.67	5.4 ± 1.56	5.6 ± 1.50
	Median	6.0	6.0	6.0	6.0
	Range	2 – 8	2 – 8	2 – 8	2 – 8
Visit 2 (baseline)	n	34	34	33	33
	Mean ± SD	0.8 ± 0.99	0.6 ± 0.92	0.8 ± 1.17	0.8 ± 1.14
	Median	0.0	0.0	0.0	0.0
	Range	0 – 3	0 – 3	0 – 4	0 – 4
Visit 3 (end of study)	n	34	34	32	32
	Mean ± SD	2.0 ± 2.41	1.9 ± 2.27	3.3 ± 3.12	3.4 ± 3.34
	Median	1.0	1.0	3.0	3.0
	Range	0 – 8	0 – 8	0 – 11	0 – 11

EASI – Eczema Area Severity Index

Frequency distribution of Investigator's Global Assessment by visit and treatment (safety population)

		Pimecrolimus cream 1% N=34	Placebo N=33
Visit 1 (screening)	Mild	16 (47.1)	12 (36.4)
	Moderate	18 (52.9)	21 (63.6)
Visit 2 (baseline)	Clear	8 (23.5)	12 (36.4)
	Almost clear	20 (58.8)	13 (39.4)

	Mild	4 (11.8)	7 (21.2)
	Moderate	2 (5.9)	1 (3.0)
Visit 3 (end of study)	Clear	7 (20.6)	2 (6.1)
	Almost clear	11 (32.4)	7 (21.2)
	Mild	8 (23.5)	9 (27.3)
	Moderate	8 (23.5)	10 (30.3)
	Severe	0 (0.0)	4 (12.1)

Safety Results

Incidence rates of overall and local common AEs (safety population)

Primary system organ class **Preferred term**	**Pimecrolimus cream 1% N=34**	**Placebo N=33**	**Total N=67**
Number of patients with at least one AE	14 (41.2)	8 (24.2)	22 (32.8)
Eye disorders	0 (0.0)	1 (3.0)	1 (1.5)
Conjunctivitis	0 (0.0)	1 (3.0)	1 (1.5)
Gastrointestinal disorders	2 (5.9)	1 (3.0)	3 (4.5)
Abdominal pain upper	1 (2.9)	1 (3.0)	2 (3.0)
Diarrhea	1 (2.9)	0 (0.0)	1 (1.5)
Hemorrhoids	1 (2.9)	0 (0.0)	1 (1.5)
Toothache	1 (2.9)	0 (0.0)	1 (1.5)
Infections and infestations	7 (20.6)	5 (15.2)	12 (17.9)
Nasopharyngitis	5 (14.7)	3 (9.1)	8 (11.9)
Gastroenteritis	1 (2.9)	0 (0.0)	1 (1.5)
Herpes simplex	1 (2.9)	0 (0.0)	1 (1.5)
Urinary tract infection	1 (2.9)	0 (0.0)	1 (1.5)
Gastroenteritis viral	0 (0.0)	1 (3.0)	1 (1.5)
Postoperative wound infection	0 (0.0)	1 (3.0)	1 (1.5)
Injury, poisoning and procedural complications	2 (5.9)	0 (0.0)	2 (3.0)
Procedural pain	1 (2.9)	0 (0.0)	1 (1.5)
Road traffic accident	1 (2.9)	0 (0.0)	1 (1.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (3.0)	1 (1.5)
Neck pain	0 (0.0)	1 (3.0)	1 (1.5)
Nervous system disorders	5 (14.7)	1 (3.0)	6 (9.0)
Headache	5 (14.7)	1 (3.0)	6 (9.0)
Lethargy	1 (2.9)	0 (0.0)	1 (1.5)
Psychiatric disorders	1 (2.9)	0 (0.0)	1 (1.5)
Insomnia	1 (2.9)	0 (0.0)	1 (1.5)
Respiratory, thoracic and mediastinal disorders	2 (5.9)	0 (0.0)	2 (3.0)
Nasal congestion	1 (2.9)	0 (0.0)	1 (1.5)
Pharyngolaryngeal pain	1 (2.9)	0 (0.0)	1 (1.5)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (6.1)	2 (3.0)
Pain of skin	0 (0.0)	1 (3.0)	1 (1.5)
Pruritus	0 (0.0)	1 (3.0)	1 (1.5)
Surgical and medical procedures	1 (2.9)	0 (0.0)	1 (1.5)

Wisdom teeth removal	1 (2.9)	0 (0.0)	1 (1.5)

A patient with multiple occurrences of a distinct AE is counted only once in the preferred term category for that treatment. A subject with multiple AEs within a primary system organ class is counted only once in that class.

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

	Pimecrolimus cream 1% (N=34)	Placebo (N=33)
At least 1 AE	41.2	24.2
AEs		
Nasopharyngitis	14.7	9.1
Headache	14.7	3.0
Abdominal pain upper	2.9	3.0
Lethargy		
Conjunctivitis	0.0	3.0
Diarrhea	2.9	0.0
Haemorrhoids	2.9	3.0
Toothache	2.9	0.0
Gastroenteritis	2.9	0.0
Herpes simplex	2.9	0.0
Urinary Tract Infection	2.9	0.0

Serious Adverse Events and Deaths

	Pimecrolimus cream 1% N=34	**Placebo N=33**	**Total N=67**
Deaths or non-fatal SAE(s)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinued due to AE(s)	0 (0.0)	0 (0.0)	0 (0.0)
Dose adjustment/temporary interruption due to AE(s)	0 (0.0)	1 (3.0)	1 (1.5)
Concomitant medication taken due to AE(s)	10 (29.4)	5 (15.2)	15 (22.4)
Non-drug therapy given due to AE(s)	1 (2.9)	0 (0.0)	1 (1.5)

No deaths were reported during this trial. No Serious Aderse Events were reported during this trial, only one SAE was reported during the follow up phase (dishydrotic eczema of the hand).

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

Ongoing

Date Inclusion on Novartis Clinical Trial Results Database

11-July-2006

Date of Latest Update

11-July-2006