Sponsor Novartis
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. Pimecrolimus 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 CASM981C2442
Title A 12 week multicenter study consisting of a 6 week double blind, randomized, vehicle controlled, parallel group phase, followed by a 6 week open label phase, to assess the safety and efficacy of pimecrolimus cream 1% in mild to moderate head and neck atopic dermatitis of patients intolerant of topical corticosteroid
Phase of Development Phase IV
Study Start/End Dates 19 October 2004 to 28 Jul 2005
Study Design/Methodology A 12 week multicenter study consisting of a 6-week double-blind, vehicle-controlled phase to assess the effect of pimecrolimus versus vehicle on head & neck, and a 6-week open-label phase to assess the safety of pimecrolimus on head & neck. The study drug (pimecrolimus or vehicle cream) was applied twice daily (b.i.d.) throughout the double-blind phase of the study. Upon completion, patients entered the open-label phase where they received pimecrolimus cream only for use twice daily on an "as needed" basis.
Centres 28 centers in 5 countries: Australia (5), Canada (5), France (5), Sweden (6), Italy (7)
Publication Ongoing

Objectives
Primary outcome/efficacy objective(s)

To determine the efficacy of pimecrolimus cream on the face of mild to moderate atopic dermatitis (AD) patients intolerant of, or dependent on, topical corticosteroids (TCS) by testing the hypothesis that a greater percentage of patients treated with pimecrolimus vs. vehicle would achieve a facial Investigator's Global Assessment (IGA) score of 0 or 1 (clear or almost clear) at the end of a 6-week period.

Secondary outcome/efficacy objective(s)

To determine the effect of pimecrolimus vs. vehicle cream on: overall Eczema Area Severity Index (EASI) score, head and neck EASI score, pruritus (itch) score, and time to clearance of facial AD at the end of 6 weeks.

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

Pimecrolimus cream 1% supplied in 50 g tubes. The treatment was to be applied topically to the affected skin area twice daily.

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

The reference therapy was administered in the same way as the test product above.

Criteria for Evaluation

Primary efficacy:

A facial IGA of 0 or 1 (clear or almost clear) score assessed at Day 43 (Week 6).

Secondary efficacy:

- Percentage of responders in overall EASI score and head and neck EASI score as assessed at Week 6
- Percentage of patients achieving at least a 60% reduction from baseline in overall EASI and head and neck EASI score were compared between the two treatment groups at Week 6
- Pruritus score at Week 6 (defined as a score of 1 or less)
- Time to clearance defined as a facial IGA score of 1 or less
- Eyelid dermatitis assessment (EDA) (as assessed at Weeks 6 where response was defined as a score of 0 on all the clinical signs: erythema [redness], lichentification [thick, leathery skin resulting of chronic scratching and rubbing], pruritus [itch], scaling/dryness and oozing/crusting)
- An exploratory analysis of the clinical evaluation of skin atrophy [skin thinning] and telangiectasia ["spider veins"] using dermatoscopy on the head and neck at Weeks 6 and 12

Safety/tolerability:

Safety assessments consisted of monitoring and recording all adverse events (AEs), serious adverse events (SAEs) (with their severity and relationship to study drug), tolerability to study drug, pulse rate and blood pressure.

Statistical Methods

All demographic and baseline characteristics were analyzed descriptively.

The primary efficacy parameter, facial IGA score, was summarized throughout the study and analyzed by means of Fisher's exact test. Summary statistics were also produced throughout the study for all secondary efficacy parameters where the

analyses were mostly performed as with the primary efficacy parameter. Kaplan-Meier estimates were produced for time to clearance of facial AD. Analyses of EDA score and dermatoscopy evaluations were also explored.

All the above analyses were performed for the intent-to-treat (ITT) population. All safety and tolerability data were summarized and presented by treatment groups for the safety population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Patients were recruited into the study if they:

- Were 12 years of age or older
- Had mild to moderate facial AD at baseline (facial IGA 2 – 3; based on assessment of the face only and excluding the ears and the neck)
- Were intolerant of, or dependent on, TCS

  Intolerance was defined as:
  - Allergic reaction or other AE that prevents the patient from using TCS to successfully treat an AD flare on the head or neck
  - Presence of rosacea, telangiectasia, and/or skin atrophy known to be a result of TCS
  - Perioral dermatitis (including perinasal and/or periorbital dermatitis) as a result of TCS usage on the face
  - Eyelid dermatitis where raised intraocular pressure was also present and/or the patient has a history of glaucoma

  Dependence was defined as:
  - Unacceptable level of recent topical corticosteroids use on the head and neck, that based on the investigator's opinion and patient's medical history may have resulted in AEs (e.g. use of TCS for at least 3 - 4 days per week to control symptoms, or at least 10 times total in the 4 weeks prior to study start)
- Had a diagnosis of AD fulfilling the Hanifin and Rajka criteria
- Had a negative pregnancy test (females only)
- Were women of child-bearing potential following a medically recognized form of contraception

Exclusion Criteria

Patients were excluded from the study if they:

- Were women who were pregnant or breast-feeding
- Had AD on greater than 30% of total body surface area in addition to facial eczema
- Had concurrent skin disease (e.g., acne) in the study area or active skin infections (active bacterial, viral or fungal infections or infestations, herpes simplex, herpes zoster, chicken pox), or other conditions that could have interfered with the evaluation (e.g., generalized erythroderma, Netherton's syndrome)
- Were immunocompromised (e.g., Lymphoma, AIDS, Wiskott-Aldrich Syndrome) or had a history of malignant disease (with the exception of treated basal-cell carcinoma)
- Had previously reported poor response, no clinical response, or hypersensitivity to topical pimecrolimus cream

- Had received phototherapy (e.g. UVA, UVB) or systemic therapy (e.g., immunosuppressants, corticosteroids, cytostatics) known or suspected to have an effect on AD within 4 weeks of Visit 2
- Had received investigational drugs within 8 weeks of first application of study drug or planned use of other investigational drugs during participation of this study
- Were unlikely to comply with therapy

	Pimecrolimus Cream n (%)	Vehicle n (%)	Total n (%)
Double blind phase			
Randomized/entered	101	99	200
Treated	101 (100.0)	99 (100.0)	200 (100.0)
Completed	74 (73.3)	39 (39.4)	113 (56.5)
Discontinued	27 (26.7)	60 (60.6)	87 (43.5)
AEs	5 (5.0)	6 (6.1)	11 (5.5)
Unsatisfactory therapeutic effect	12 (11.9)	44 (44.4)	56 (28.0)
Patient's condition no longer required study drug	6 (5.9)	1 (1.0)	7 (3.5)
Protocol violation	1 (1.0)	2 (2.0)	3 (1.5)
Patient withdrew consent	1 (1.0)	5 (5.1)	6 (3.0)
Lost to follow-up	2 (2.0)	2 (2.0)	4 (2.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

	Pimecrolimus Cream/ Pimecrolimus Cream n (%)	Vehicle/ Pimecrolimus Cream n (%)	Total n (%)
Open label phase			
Entered open label phase	89	67	156
Completed	78 (87.6)	62 (92.5)	140 (89.7)
Discontinued	11 (12.4)	5 (7.5)	16 (10.3)
AEs	1 (1.1)	0 (0.0)	1 (0.6)
Unsatisfactory therapeutic effect	4 (4.5)	3 (4.5)	7 (4.5)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	3 (3.4)	1 (1.5)	4 (2.6)
Lost to follow-up	2 (2.2)	1 (1.5)	3 (1.9)
Administrative problems	1 (1.1)	0 (0.0)	1 (0.6)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Denominator for the percentage is the number of patients entered in the phase.

Number of Subjects

Demographic and Background Characteristics

Demographic variable	Pimecrolimus Cream (N=101)	Vehicle (N=99)	Total (N=200)
Age (years)			
n	101	99	200
Mean (SD)	33.8 (15.42)	32.7 (15.80)	33.3 (15.58)
Median	32.0	28.0	30.5
Min - Max	12 - 78	12 - 81	12 - 81
Age group - n(%)			
<18 years	15 (14.9)	18 (18.2)	33 (16.5)
18-<40 years	57 (56.4)	51 (51.5)	108 (54.0)
40-<65 years	23 (22.8)	26 (26.3)	49 (24.5)
>=65 years	6 (5.9)	4 (4.0)	10 (5.0)
Sex - n(%)			
Male	44 (43.6)	33 (33.3)	77 (38.5)
Female	57 (56.4)	66 (66.7)	123 (61.5)
Race - n(%)			
Caucasian	89 (88.1)	86 (86.9)	175 (87.5)
Black	2 (2.0)	1 (1.0)	3 (1.5)
Oriental	6 (5.9)	8 (8.1)	14 (7.0)
Other	4 (4.0)	4 (4.0)	8 (4.0)

Denominator for the percentage calculation is the number of patients in the safety population.

Primary Efficacy Result(s)

Visit	Response	Pimecrolimus Cream (N=101)	Vehicle (N=99)	P-value [1]
Day 8	Facial IGA <= 1	21 (20.8)	7 (7.1)	0.0073
	Facial IGA > 1	80 (79.2)	92 (92.9)	
Day 22	Facial IGA <= 1	40 (39.6)	13 (13.1)	<0.001
	Facial IGA > 1	61 (60.4)	86 (86.9)	
Day 43 [2]	Facial IGA <= 1	47 (46.5)	16 (16.2)	<0.001
	Facial IGA > 1	54 (53.5)	83 (83.8)	

[1] Fisher's exact test of difference in proportions between treatment groups.
[2] Day 43 is the primary visit of interest

Secondary efficacy result(s)

EASI responder assessment – head & neck

Visit	Pimecrolimus Cream 1% (N=101)	Vehicle (N=99)	P-value [1]
Day 8 n (%)	28 (27.7)	4 (4.0)	<0.001
Day 22 n (%)	46 (45.5)	14 (14.1)	<0.001
Day 43 [2]	51 (50.5)	18 (18.2)	<0.001

Treatment responder was defined as at least a 60% change from baseline in head and neck EASI score.
[1] Fisher's exact test of difference in proportions between treatment groups.
[2] Day 43 is the primary visit of interest.

EASI assessment – overall

Visit	Pimecrolimus Cream 1% (N=101)	Vehicle (N=99)	P-value [1]
Day 8	21 (21.0)	3 (3.0)	<0.001
Day 22	29 (28.7)	11 (11.1)	0.0024
Day 43 [2]	39 (38.6)	17 (17.2)	<0.001

Treatment responder was defined as at least a 60% change from baseline in overall EASI score.
[1] Fisher's exact test of difference in proportions between treatment groups.
[2] Day 43 is the primary visit of interest.

Pruritus Assessment:

Visit	Response	Pimecrolimus Cream 1% (N=101)	Vehicle (N=99)	P-value [1]
Baseline	Pruritus <= 1	27 (26.7	25 (25.2)	
	Pruritus > 1	74 (73.3)	74 (74.7)	
Day 8	Pruritus <= 1	61 (60.4)	33 (33.3)	<0.001
	Pruritus > 1	40 (39.6)	66 (66.7)	
Day 22	Pruritus <= 1	70 (69.3)	37 (37.4)	<0.001
	Pruritus > 1	31 (30.7)	62 (62.6)	
Day 43 [2]	Pruritus <= 1	70 (69.3)	34 (34.3)	<0.001
	Pruritus > 1	31 (30.7)	65 (65.7)	

Note: Pruritus severity: 1=mild, 2=moderate, 3=severe
[1] Fisher's exact test of difference in proportions between treatment groups.
[2] Day 43 is the primary visit of interest.

Time to clearance:

Kaplan-Meier estimates for time to clearance (i.e. IGA of 0 or 1) based on facial IGA

	Pimecrolimus cream	Vehicle	

	(N=101)	(N=99)	
Kaplan-Meier estimate			
Mean (SE)	32.5 (1.78)	41.4 (1.51)	
Median	43.0	N/A	

Eyelid Dermatitis assessment:

Summary of dichotomized eyelid dermatitis score * by visit (DB, ITT population, Last Observation Carried Forward)

	Pimecrolimus cream		Vehicle cream		Total		
Visit	N	Success(%)	N	Success(%)	N	Success(%)	P-value [1]
Day 1 (Baseline)	100	19(19.0)	98	15(15.3)	198	34(17.2)	0.5731
Day 43	101	45 (44.6)	99	19 (19.2)	200	64 (32.0)	<0.001

*Success is defined as scoring 0 on all clinical signs: erythema, lichenification, pruritus, scaling/dryness, and oozing/crusting. [1] Effect of treatment from Fisher's exact test.

Skin atrophy and telangiectasia assessment:

Between-group analysis of skin atrophy and telangiectasia (DB, ITT population, Last Observation Carried Forward)

Assessment	Day	N	P-value[1]
Skin Atrophy	43	199	0.8764
Telangiectasia	43	199	0.6400

[1] Effect of treatment from Wilcoxon rank sum test.

Within-group analysis of skin atrophy and telangiectasia (DB, ITT population, Last Observation Carried Forward)

Assessment	Treatment	Day	N	P-value [1]
Skin Atrophy	Pimecrolimus cream	43	100	0.0094
	Vehicle	43	99	1.0000
	Total	43	199	0.0336
Telangiectasia	Pimecrolimus cream	43	100	0.0290
	Vehicle	43	99	0.3833
	Total	43	199	0.0186

[1] P-value is for sign test comparing the specified visit with baseline.

Between-group analysis of change from baseline skin atrophy and telangiectasia for patients having the sign/symptoms at baseline (DB, ITT population, LOCF)

Assessment	Day	N	P-value [1]
Skin Atrophy	43	77	0.0214
Telangiectasia	43	112	0.9537

[1] Effect of treatment from Wilcoxon rank sum test.

Safety Results

Incidence rates of all treatment emergent adverse events by body system and treatment (DB, Safety population)

Primary system organ class	Pimecrolimus cream (Days studied=2646) n=events (*)	Vehicle (Days studied=1463) n=events (*)	Total (Days studied=4109) n=events (*)
Any primary system organ class	224 (84.7)	171 (116.9)	395 (96.1)
General disorders and administration site conditions	138 (52.2)	109 (74.5)	247 (60.1)
Infections and infestations	25 (9.4)	17 (11.6)	42 (10.2)
Nervous system disorders	16 (6.0)	9 (6.2)	25 (6.1)
Skin and subcutaneous tissue disorders	8 (3.0)	8 (5.5)	16 (3.9)
Respiratory, thoracic and mediastinal disorders	7 (2.6)	3 (2.1)	10 (2.4)
Vascular disorders	7 (2.6)	0 (0.0)	7 (1.7)
Psychiatric disorders	6 (2.3)	2 (1.4)	8 (1.9)
Gastrointestinal disorders	5 (1.9)	10 (6.8)	15 (3.7)
Eye disorders	4 (1.5)	7 (4.8)	11 (2.7)
Reproductive system and breast disorders	4 (1.5)	1 (0.7)	5 (1.2)
Injury, poisoning and procedural complications	2 (0.8)	0 (0.0)	2 (0.5)
Metabolism and nutrition disorders	1 (0.4)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1** (0.4)	0 (0.0)	1 (0.2)
Cardiac disorders	0 (0.0)	1 (0.7)	1 (0.2)
Ear and labyrinth disorders	0 (0.0)	1 (0.7)	1 (0.2)
Immune system disorders	0 (0.0)	2 (1.4)	2 (0.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.7)	1 (0.2)

* Incidence density of an adverse event per 1,000 patient-days is defined as the number of occurrences of that adverse event (k) divided by total number of days during which patients were studied, multiplied by 1,000 according to the following formulae; [(k/days in the DB phase of the study) x 1,000]

** One case of hygroma colli (Preferred term)

Incidence rates of common (rate >=2 in any treatment group) treatment emergent adverse events (DB, Safety population)

Primary system organ class Preferred term	Pimecrolimus cream (Days studied=2646) n= events (*)	Vehicle (Days studied=1463) n= events (*)	Total (Days studied=4109) n= events (*)
Any primary system organ class	224 (84.7)	171 (116.9)	395 (96.1)

General disorders and administration site conditions	138 (52.2)	109 (74.5)	247 (60.1)
Application site irritation	38 (14.4	31 (21.2)	69 (16.8)
Application site warmth	22 (8.3)	12 (8.2)	34 (8.3)
Application site pruritus	17 (6.4)	8 (5.5)	25 (6.1)
Application site pain	15 (5.7)	24 (16.4)	39 (9.5)
Application site erythema	13 (4.9)	16 (10.9)	29 (7.1)
Application site reaction	6 (2.3)	1 (0.7)	7 (1.7)
Application site paraesthesia	5 (1.9)	3 (2.1)	8 (1.9)
Application site oedema	1 (0.4)	3 (2.1)	4 (1.0)
Application site swelling	0 (0.0)	5 (3.4)	5 (1.2)
Infections and infestations	25 (9.4)	17 (11.6)	42 (10.2)
Influenza	6 (2.3)	2 (1.4)	8 (1.9)
Nasopharyngitis	6 (2.3)	5 (3.4)	11 (2.7)
Nervous system disorders	16 (6.0)	9 (6.2)	25 (6.1)
Headache	13 (4.9)	5 (3.4)	18 (4.4)
Migraine	1 (0.4)	4 (2.7)	5 (1.2)
Skin and subcutaneous tissue disorders	8 (3.0)	8 (5.5)	16 (3.9)
Pruritus	0 (0.0)	3 (2.1)	3 (0.7)
Respiratory, thoracic and mediastinal disorders	7 (2.6)	3 (2.1)	10 (2.4)
Vascular disorders	7 (2.6)	0 (0.0)	7 (1.7)
Flushing	7 (2.6)	0 (0.0)	7 (1.7)
Psychiatric disorders	6 (2.3)	2 (1.4)	8 (1.9)
Gastrointestinal disorders	5 (1.9)	10 (6.8)	15 (3.7)
Eye disorders	4 (1.5)	7 (4.8)	11 (2.7)

* Incidence density of an adverse event per 1,000 patient-days is defined as the number of occurrences of that adverse event (k) divided by total number of days during which patients were studied, multiplied by 1,000 according to the following formulae; [(k/days in the DB phase of the study) x 1,000].

During the DB phase, the majority of AEs were mild or moderate in severity. The moderate and severe AEs were predominantly application site conditions (moderate 14.9% vs. 18.2% of patients and severe 7.9% vs. 11.1% of patients, respectively). The incidence of moderate and severe AEs was generally similar between groups although application site reactions of higher severity were slightly more common in the vehicle group.

Adverse Event incidence density rate:

Adverse event incidence density rate was expressed as the number of individual AEs and total numbers per 1,000 days on treatment. This analysis takes into account the fact that there was a higher rate of patients leaving the study in the vehicle group. The incidence densities of AEs in the pimecrolimus and vehicle groups was 84.7 and 116.9 AEs per 1,000 days, respectively, compared with 71.3% and 60.6%, respectively, for the crude incidence. The incidence of application site reactions was lower in the pimecrolimus group than in the vehicle group. The most frequent of these was irritation, with incidence densities of 14.4 and 21.2 AEs per 1,000 days, respectively. Similarly, for infections and infestations the incidence was lower in the pimecrolimus group (9.4 and 11.6 AEs per1,000 days, respectively).

Adverse events suspected to be related to study drug

Overall, during the DB phase, 43.6% of patients receiving pimecrolimus and 46.5% of patients receiving vehicle had AEs which were suspected to be related to study drug. Application site reactions were the most common in both groups. Other more frequent suspected AEs included infections and infestations (mainly nasopharyngitis and upper respiratory infection) and nervous system disorders. The general incidence of these suspected AEs was similar for both groups, indicating no apparent toxicities or reactions resulting from pimecrolimus or vehicle alone.

The incidence of head and neck application site reactions considered to be caused by the study drug varied with time. For the pimecrolimus and vehicle groups, respectively, such reactions caused by the treatment were reported in 10.9% and 12.1% of patients at Day 1, in 21.8% and 26.3% at Day 8, and 6.9% and 2.0% at Day 43. These were consistent with a general increase in the number of patients with reactions due to any cause at Day 8, which then decreased at Days 22 and 43.

During the OL phase, AEs suspected to be related to study drug were reported in 12.8% of patients.

Serious Adverse Events and Deaths

Significant AE	Pimecrolimus Cream/ Pimecrolimus Cream n (%)	Vehicle/ Pimecrolimus Cream n (%)	Total n (%)
Double blind phase	101	99	200
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 SAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations due to AE	5 (5.0)	6 (6.1)	11 (5.5)
Open label phase	89	67	156
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
At least 1 SAE	1 (1.1)	0 (0.0)	1 (0.6)
Discontinuations due to AE	1 (1.1)	0 (0.0)	1 (0.6)

Denominator for each phase is the number of patients who entered that phase.

There were no deaths or SAEs during the DB phase of the study. No deaths were reported during the OL phase, but there was one SAE (hand fracture) in the pimecrolimus/pimecrolimus arm.

Date of Clinical Trial Report

17 November 2005

Date Inclusion on Novartis Clinical Trial Results Database

18 October 2006

Date of Latest Update

October 2006