Sponsor

Novartis

Generic Drug Name

Pimecrolimus

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 cream 1% is approved in the following countries: Albania, Argentina, Armenia, Aruba, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Belarus, Belgium, Bosnia-Herzegovina, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Ghana, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Israel, Italy, Jamaica, Jordan, Kazakhstan, Kenya, Korea, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Macedonia, Malaysia, Malta, Mexico, Moldova, Morocco, Netherlands, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Palestine, Panama, Peru, Philippines, Poland, Portugal, Qatar, Republika Srpska, Romania, Russia, Saudi-Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Tanzania, Thailand, Trinidad & Tobago, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, Uzbekistan, Venezuela, Yemen

Study Number

CASM981CDE20 (REPIDEL)

Title

An uncontrolled, multicenter 12-month long-term study on skin reconstitution with pimecrolimus 1% cream in adult patients with atopic eczema and corticosteroid induced skin damage

Phase of Development

Phase IV

Study Start/End Dates

22 Mar 2006 to 20 Dec 2007

Study Design/Methodology

This was a single-group, open-label study. Patients received intermittent treatment with pimecrolimus 1% cream for one year and steroid rescue medication, if necessary. At the baseline visit, patients whose eligibility was confirmed were enrolled into the study and entered a 12-month treatment phase. Skin reconstitution, disease control and safety were assessed after 4 and 12 weeks and at 12-weekly intervals until Week 48. The evaluation of the primary objective was performed at the end of the study. An additional visit following 4 weeks after a major flare (i.e., after end of prednicarbate rescue medication) was planned to take place, if a major flare occurred between weeks 44 and 48. In this case, the study duration was allowed to be extended to up to 52 weeks. If a major flare occurred close to Week 48, the prednicarbate therapy had to be shortened in order not to exceed Week 48.

Centres

Four centers in Germany

Publication

Ongoing

Objectives

Primary objective(s)

- To investigate the reconstitution of steroid damaged skin with pimecrolimus 1% cream by assessing the decrease of the Dermatophot® score from baseline to end of the study.

Secondary objective(s)

- To investigate the reconstitution of steroid damaged skin with pimecrolimus 1% cream by measurement of epidermal thickness with optical coherence tomography (OCT) at selected centers
- To investigate the reconstitution of steroid damaged skin with pimecrolimus 1% cream by measurement of skin thickness with ultrasound at selected centers
- To investigate the control of atopic eczema with pimecrolimus 1% cream with the Investigator's Global Assessment (IGA)
- To assess safety and tolerability

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

- Pimecrolimus 1% cream
- 48-52 weeks of variable treatment according to the guidelines on the long-term management of atopic dermatitis was applied in this study to all patients.

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

- Prednicarbate cream 0.25% rescue therapy
- 48-52 weeks of variable treatment according to the guidelines on the long-term management of atopic dermatitis was applied in this study to all patients.

Criteria for Evaluation

Primary variables

Decrease of the Dermatophot® score from baseline to end of the study

Secondary variables

- Measurement of epidermal thickness with optical coherence tomography (OCT) at selected centers; change from baseline to week 4, week 12, week 24, week 36 and week 48 (or final visit)
- Measurement of skin thickness with ultrasound at selected centers; change from baseline to week 4, week 12, week 24, week 36 and week 48 (or final visit)
- Investigator's Global Assessment (IGA); change from baseline to week 4, week 12, week 24, week 36 and week 48 (or final visit)

Safety and tolerability

Type, frequency and severity of AEs

Pharmacology

None

Other

None

Statistical Methods

The following populations were defined to analyze the trial data:

- Safety and tolerability evaluations were performed using the sample of all patients who applied study medication at least once (safety population).
- The intention-to-treat (ITT) population consisted of all patients from the safety population if they have at least one post-baseline assessment of the primary endpoint.

The ITT population was used for the primary efficacy analysis.

Descriptive statistics of subject characteristics and baseline values were presented for all populations.

The primary endpoint was the change of the Dermatophot® score between baseline and end of study.

The primary analysis was performed using a one-sample, two-sided t-test to test the null hypothe-

sis of no change of the Dermatophot® score between baseline and end of study against the alternative of a change ≠ 0. The result was presented as means together with a 95% confidence interval and a p-value for the null-hypothesis of no change.

Significance Level: The primary analysis was performed on the two-sided 5% level.

Missing values of the Dermatophot® score at baseline were not expected, missing values of the Dermatophot® score after baseline were replaced by the last observed value of that patient (LOCF). Missing values at baseline were replaced by the next observed value of that patient (LOCB).

Missing values of other parameters were not replaced.

The primary analysis was repeated using a non-parametric test (Wilcoxon) as well as for the PP population.

All continuous secondary endpoints were analyzed analogous to the primary endpoint. Changes in discrete secondary endpoints were presented as summary frequency tables.

35 patients were required to detect a change with > 80% power using a one-sample t-test on a two-sided 5% significance level, if the true mean change exceeded 50% of its standard deviation. Such an effect size was usually referred to as a medium sized effect and would be worth detecting. To compensate for drop-outs, target enrollment was 40 patients

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients were eligible for inclusion if they met all of the following criteria:

- Between 18 and 60 years of age.
- Clinically diagnosed atopic dermatitis according to Hanifin and Rajka.
- Local Investigator's Global Assessment (IGA) on at least two target lesions (face and cubital areas): 1-3.
- Clinically (naked eye) evident skin atrophy due to long term topical steroid use.
- Dermatophot® Score of 4-6 on at least two target areas.

Patients were to be excluded from participation if they met any of the following criteria:

- Acute major flare condition.
- Phototherapy (e.g., UVB, PUVA) or systemic therapy (e.g., immunosuppressants, cytostatics) known or suspected to have an effect on AD within 4 weeks prior to study entry.
- Topical therapy [e.g., topical steroids, tar, pimecrolimus 1% cream, tacrolimus ointment] known or suspected to have an effect on AD within 7 days prior to study entry, or systemic corticosteroids (i.e., oral, intravenous, intraarticular, rectal) within 4 weeks prior to study entry. Patients on a stable maintenance dose of inhaled corticosteroids were allowed to participate.
- Presence of clinical conditions other than AD that according to investigator can interfere with the Dermatophot® evaluation (e.g., generalized erythroderma such as the genetic condition Netherton's syndrome, other skin conditions such as psoriasis).
- History of malignancy of any organ system, treated or untreated whether or not there is evidence of local recurrence or metastases.

- Systemic immunosuppression.
- Clinical signs of infection in the treatment area.
- History of hypersensitivity to pimecrolimus 1% cream or prednicarbate or to drugs with similar chemical structures and/or to any other ingredients of the formulation.
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG test. Females of childbearing potential and not practicing a medically approved method of contraception during and up to at least 4 weeks after the end of treatment. 'Medically approved' contraception may include implants, injectables, combined oral contraceptives, intrauterine devices, but also abstinence at the discretion of the investigator.
- Use of other investigational drugs within 30 days of enrollment.

Number of Subjects	
	Total n (%)
Planned N	41
Randomized n	41
Completed n (%)	34 (82.9)
Withdrawn n (%)	7 (17.1)
Included in the primary analysis n (%)	41
Withdrawn due to adverse events n (%)	0
Withdrawn due to lack of efficacy n (%)	4 (9.8)
Withdrawn for other reasons n (%)	3 (7.2)
Demographic and Background Characteristics	
	Total n (%)
N (ITT)	41
Females:males	18:23 (43.9:56.1)
Mean age, years (SD)	35.9 (13.7)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 40 (97.6) 0 (0) 0 (0) 1 (2.4)

Primary Objective Result(s)

Changes in Dermatophot® score from Baseline to Week 48 (ITT population)

Location	Statistic	Baseline	Week 48	Abs. change	Rel. change [%]
Face	N	41	41	41	41
	Mean	4.9	3.5	-1.4	-30.5
	SD	0.9	1.8	1.5	30.6
	Minimum	3.0	1.0	-5.0	-83.3
	Median	5.0	3.0	-2.0	-40.0
	Maximum	6.0	7.0	1.0	25.0

	95%-CI for the mean	-	-	-1.9; -1.0	-40.1; -20.8
	P (t-test)	-	-	<0.0001	<0.0001
	P (Wilcoxon-test)	-	-	<0.0001	<0.0001
Cubital area	N	41	41	41	41
	Mean	4.3	2.7	-1.7	-38.6
	SD	0.6	1.5	1.4	33.0
	Minimum	4.0	0.0	-4.0	-100.0
	Median	4.0	3.0	-2.0	-40.0
	Maximum	6.0	6.0	2.0	50.0
	95%-CI for the mean	-	-	-2.1; -1.2	-49.0; -28.2
	P (t-test)	-	-	<0.0001	<0.0001
	P (Wilcoxon-test)	-	-	<0.0001	<0.0001

Subgroup analysis of the changes in Dermatophot® score from Baseline to Week 48 (ITT population)

Location	Subgroup [a]	Statistics	Abs. change	Rel. change [%]
Face	**≤ 33% exposure to rescue med.**	N	20	20
		Mean	-1.6	-35.9
		SD	1.4	29.7
		95%-CI for the mean	-2.3; -0.9	-49.8; -22.0
		P (t-test)	<0.0001	<0.0001
		P (Wilcoxon-test)	0.0002	0.0001
	> 33% exposure to rescue med.	N	21	21
		Mean	-1.3	-25.3
		SD	1.6	31.2
		95%-CI for the mean	-2.0; -0.6	-39.5; -11.1
		P (t-test)	0.0014	0.0014
		P (Wilcoxon-test)	0.0013	0.0015
Cubital area	**≤ 33% exposure to rescue med.**	N	20	20
		Mean	-1.9	-44.3
		SD	1.5	35.6
		95%-CI for the mean	-2.6; -1.2	-60.9; -27.6
		P (t-test)	<0.0001	<0.0001
		P (Wilcoxon-test)	0.0002	0.0002
	> 33% exposure to rescue med.	N	21	21
		Mean	-1.4	-33.2
		SD	1.3	30.2
		95%-CI for the mean	-2.0; -0.8	-46.9; -19.4
		P (t-test)	<0.0001	<0.0001
		P (Wilcoxon-test)	0.0002	0.0002

[a]Percentages refer to the relative extent (time) of exposure to rescue medication during the study period. Note: The LOCF method was applied.

Categorical analyses of Dermatophot® scores (ITT population)

Location	Characteristic	Assessment	Baseline n (%)	Week 48 n (%)
Face:	**Atrophy**	No change compared to normal skin	0 (0.0)	3 (7.3)
		Slight transparency	2 (4.9)	18 (43.9)
		Moderate thinning of the epidermis with moderate increase in transparency	26 (63.4)	12 (29.3)
		Severe thinning and increase in transparency	13 (31.7)	8 (19.5)
		Very severe thinning of the epidermis	0 (0.0)	0 (0.0)
	Telangiectasia	Normal vascular pattern	0 (0.0)	2 (4.9)
		Capillary hyperemia with slight elongation and dilatation of blood vessels	2 (4.9)	16 (39.0)
		Moderate telangiectasia	16 (39.0)	12 (29.3)
		Severe telangiectasia	18 (43.9)	8 (19.5)
		Very severe telangiectasia with large blunt vessels	5 (12.2)	3 (7.3)
Cubital area:	**Atrophy**	No change compared to normal skin	0 (0.0)	4 (9.8)
		Slight transparency	0 (0.0)	19 (46.3)
		Moderate thinning of the epidermis with moderate increase in transparency	28 (68.3)	15 (36.6)
		Severe thinning and increase in transparency	13 (31.7)	3 (7.3)
		Very severe thinning of the epidermis	0 (0.0)	0 (0.0)
	Telangiectasia	Normal vascular pattern	0 (0.0)	7 (17.1)
		Capillary hyperemia with slight elongation and dilatation of blood vessels	4 (9.8)	21 (51.2)
		Moderate telangiectasia	32 (78.0)	8 (19.5)
		Severe telangiectasia	5 (12.2)	5 (12.2)
		Very severe telangiectasia with large blunt vessels	0 (0.0)	0 (0.0)

Secondary Objective Result(s)

Categorical changes in IGA from baseline to Week 48 (ITT population)

Location	Assessment	Baseline n (%)	Week 48 n (%)
Face	Not done	0	7
	Clear	0 (0.0)	11 (32.4)
	Almost clear	8 (19.5)	9 (26.5)
	Mild	18 (43.9)	9 (26.5)
	Moderate	13 (31.7)	4 (11.8)
	Severe	2 (4.9)	1 (2.9)
	Very severe	0 (0.0)	0 (0.0)
Cubital area	Not done	0	7
	Clear	0 (0.0)	10 (29.4)
	Almost clear	5 (12.2)	11 (32.4)
	Mild	16 (39.0)	5 (14.7)
	Moderate	18 (43.9)	8 (23.5)
	Severe	2 (4.9)	0 (0.0)
	Very severe	0 (0.0)	0 (0.0)
Global	Not done	0	7
	Clear	0 (0.0)	0 (0.0)
	Almost clear	3 (7.3)	17 (50.0)
	Mild	13 (31.7)	9 (26.5)
	Moderate	21 (51.2)	5 (14.7)
	Severe	4 (9.8)	3 (8.8)
	Very severe	0 (0.0)	0 (0.0)

Change in IGA from Baseline to Week 48 (ITT population)

Location	Assessment	Week 48 n (%)
Face	Not done	7
	Worsened	3 (8.8)
	Unchanged	9 (26.5)
	Improved	22 (64.7)
	Success	17 (50.0)
Cubital area	Not done	7
	Worsened	2 (5.9)
	Unchanged	8 (23.5)
	Improved	24 (70.6)
	Success	20 (48.8)
Global	Not done	7
	Worsened	3 (8.8)

	Unchanged	11 (32.4)
	Improved	20 (58.8)
	Success	21 (51.2)

Optical coherence tomography and ultrasound: Changes in epidermal thickness from Baseline to Week 48 (ITT population)

Method / Location	Statistics	Baseline	Abs. change at Week 48	Rel. change at Week 48 [%]
Optical coherence tomography				
Face	N	10	9	9
	Mean (µm)	60.7	-7.7	-10.2
	SD	9.1	13.4	20.7
	Minimum (µm)	47.6	-26.0	-38.6
	Median (µm)	61.3	0.7	1.2
	Maximum (µm)	75.9	9.9	19.8
	95%-CI for the mean	-	-18.0; 2.6	-26.1; 5.7
	P (t-test)	-	0.1243	0.1779
	P (Wilcoxon-test)	-	0.4023	0.4258
Cubital area	N	9	7	7
	Mean (µm)	67.2	-1.9	2.1
	SD	14.7	16.9	25.7
	Minimum (µm)	44.4	-26.9	-31.0
	Median (µm)	62.8	-2.3	-2.8
	Maximum (µm)	86.7	16.1	36.3
	95%-CI for the mean	-	-17.5; 13.7	-21.7; 25.9
	P (t-test)	-	0.7789	0.8375
	P (Wilcoxon-test)	-	0.8125	1.0000
Ultrasound				
Face	N	11	10	10
	Mean (µm)	91.6	41.2	64.4
	SD	41.1	20.1	48.3
	Minimum (µm)	26.0	8.0	7.0
	Median (µm)	86.0	43.0	53.5
	Maximum (µm)	180.0	74.0	157.4
	95%-CI for the mean	-	26.8; 55.60	29.9; 98.9
	P (t-test)	-	0.0001	0.0022
	P (Wilcoxon-test)	-	0.0020	0.0020
Cubital area	N	11	10	10
	Mean (µm)	132.8	22.1	19.9
	SD	26.0	20.3	21.2
	Minimum (µm)	97.0	2.0	1.3
	Median (µm)	139.0	13.0	9.5

	Maximum (μm)	165.0	59.0	60.8
	95%-CI for the mean	-	7.6; 36.6	4.7; 35.1
	P (t-test)	-	0.0074	0.0157
	P (Wilcoxon-test)	-	0.0020	0.0020

Safety Results

Adverse Events by System Organ Class

Overall	**Total n (%)**
No. (%) of patients studied	41 (100.0)
No. (%) of patients with AE(s)	34 (82.9)
System organ class affected / preferred term	
Ear and labyrinth disorders	2 (4.9)
Gastrointestinal disorders	6 (14.6)
Toothache	*3 (7.3)*
General disorders and administration site disorders	1 (2.4)
Infections and infestations	28 (68.3)
Nasopharyngitis	*21 (51.2)*
Injury, poisoning and procedural complications	3 (7.3)
Musculoskeletal and connective tissue disorders	6 (14.6)
Back pain	*2 (4.9)*
Neoplasms benign, malignant and unspecified	1 (2.4)
Nervous system disorders	9 (22.0)
Headache	*8 (19.5)*
Migraine	*2 (4.9)*
Sciatica	*4 (9.8)*
Psychiatric disorders	2 (4.9)
Respiratory, thoracic and mediastinal disorders	1 (2.4)
Skin and subcutaneous tissue disorders	8 (19.5)
Dermatitis atopic	*5 (12.2)*
Vascular disorders	1 (2.4)

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

	Total n (%)
Nasopharyngitis	21 (51.2)
Headache	8 (19.5)
Dermatitis atopic	5 (12.2)
Sciatica	4 (9.8)
Toothache	3 (7.3)
Back pain	2 (4.9)
Dysmenorrhoea	2 (4.9)
Migraine	2 (4.9)
Oral herpes	2 (4.9)
Abdominal pain upper	1 (2..4)

Serious Adverse Events and Deaths

Pat. no.	Preferred term	Severity	Duration [days]	Action taken
1/04	Inguinal hernia	moderate	11	• Dose adjusted/temporarily interrupted • Concomitant medication • Non-drug therapy • Hospitalization (prolonged)
1/09	Dermatitis atopic	severe	(ongoing)	• Hospitalization (prolonged)
2/18	Dermatitis atopic	severe	28	• Dose adjusted/temporarily interrupted • Concomitant medication
3/09	Subcutaneous abscess	moderate	22	• Concomitant medication • Hospitalization (prolonged)
4/05	Dermatitis atopic	severe	8	• Concomitant medication • Hospitalization (prolonged)
	Bacterial superinfection	severe	8	• None

Other Relevant Findings

None

Date of Clinical Trial Report

16. April 2008

Date Inclusion on Novartis Clinical Trial Results Database

19 November 2008

Date of Latest Update

19 November 2008