Sponsor

Novartis

Generic Drug Name

Pimecrolimus

Therapeutic Area of Trial

Perioral 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

CASM981CDE15

Title

A 4-week, randomized, vehicle-controlled, multicenter evaluation of the efficacy and safety of 1% pimecrolimus cream in adult patients with perioral dermatitis followed by a 8 week treatment free observation phase in responders.

Phase of Development

Phase III

Study Start/End Dates

27 Sep 2005 to 06 Jul 2006

Study Design/Methodology

Multicenter, double-blind, randomized, parallel group trial, using pimecrolimus cream 1% and its corresponding vehicle. Randomized patients were treated with study medication twice daily (in the morning and in the evening) for a maximum of 4 weeks or until a Perioral Disease Severity Index (PODSI) score of 0 (complete clearance) was obtained.

Centres

21 centers in Germany

Publication

Ongoing

Objectives

Primary objective(s)

To investigate the efficacy of pimecrolimus cream 1% in patients with perioral dermatitis in the mean reduction of the PODSI score (Perioral Dermatitis Severity Index) at weeks 1, 2 and 4 of treatment compared to its vehicle.

Secondary objective(s)

- Time to disease recurrence. Disease recurrence is defined as an increase in PODSI by > 50% of the PODSI decrease from baseline;
- Time to response. Response is defined as a decrease in PODSI by >= 50% of the baseline value
- Responder rates at day 8, day 15 and day 29 and in the follow-up period
- The patients' quality of life by using the Dermatology Life Quality Index by Finlay
- The patients' subjective perception of disease severity by using a visual analogue scale

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

Pimecrolimus cream 1%, applied topically twice daily to affected area

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

Vehicle cream applied topically twice daily to affected area

Criteria for Evaluation

Primary variables

Mean change from baseline of the PODSI score measured at visits 2, 3 and 4

Secondary variables

- Time to disease recurrence, defined as an increase in PODSI by > 50% of the PODSI decrease from baseline
- Time to response as defined by an increase in PODSI of >= 50% from baseline
- Responder rates at weeks Day 8, Day 15 and Day 29, as well as in the follow-up period
- Dermatology Life Quality Index (DLQI) at Baseline Day 1, Day 8, Day 15, Day 29
- Visual analogue scale (VAS) for the patients' subjective severity assessment

Safety and tolerability

Type, frequency and severity of AEs

Pharmacology

None

Other

None

Statistical Methods

The primary analysis was performed comparing treatments with respect to the primary efficacy variable in an analysis of covariance (ANCOVA) model with the factors treatment, center and covariate baseline symptom score. Results are presented as unadjusted and adjusted means together with a 95% confidence interval and a p-value for the null-hypothesis of no treatment difference. In a secondary analysis the model of the primary analysis was applied to the PODSI scores measured at each individual visit (including follow up) as well as for the individual score items for erythema, papulation and scaling. Results are presented in tabular and graphical form. Explorative subgroup analyses were performed on subgroups defined by age class, sex and prior steroid use. Handling of missing values: Missing values of the PODSI-score after baseline were replaced by the last observed value of that patient. Missing values of other parameters were not replaced. The time to response and the time to disease recurrence were graphically analysed by the method of Kaplan-Meier, treatments were compared using a log rank-test. For the responder

rates, absolute and relative frequencies are presented together with a confidence interval and a p-value both for the rate difference and for the odds ratio. The QoL (DLQI) and the VAS variables were analyzed analogously to the primary endpoint.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patients aged 18 years and older
- Clinically diagnosed with perioral dermatitis associated or not associated with topical steroid use
- A minimum severity score Perioral Disease Severity Index (PODSI) >= 4.

Exclusion criteria

- Ongoing use of the following treatments is NOT allowed after the start of study drug:
- Oral tetracyclines, oral erythromycin, oral steroids and oral calcineurin inhibitors. All topical treatments of the face, including steroids, calcineurin inhibitors, metronidazole, tetracyclines, erythromycin and emollients (exception: DAC Basiscreme, sunscreen, make-up).
- Systemic immunosuppression
- History of malignancy of any organ system, treated or untreated, within the past 5 years
- Concomitant skin disease in the study area that could interfere with evaluation of PD
- Clinical signs of infection in the treatment area
- History of hypersensitivity to pimecrolimus 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, IUDs, but also abstinence at the discretion of the investigator.
- Use of other investigational drugs within 30 days of enrollment
- Use of pimecrolimus within four weeks of enrollment
- A history of lupoid peroral dermatitis

Number of Subjects

	Pimecrolimus cream	Vehicle cream
Planned N	60	60
Randomised n	60	64
Intent-to-treat population (ITT) n (%)	60 (100)	64 (100)
Completed n (%)	56 (93.3)	56 (87.5)
Withdrawn n (%)	4 (6.7)	8 (12.5)
Withdrawn due to adverse events n (%)	1 (1.7)	4 (6.3)
Withdrawn due to lack of efficacy n (%)	2 (3.3)	1 (1.6)
Withdrawn for other reasons n (%)	1 (1.7)	3 (4.7)

Demographic and Background Characteristics

	Pimecrolimus cream	Vehicle cream
N (ITT)	60	64
Females : males	91.7: 8.3	82.8: 17.2
Mean age, years (SD)	41.8 (13.0)	44.0 (15.3)
Race White n (%) Black n (%) Asian n (%) Other n (%)	 57 (95) 0 3 (5.0) 0	 63 (98.4) 0 0 1 (1.6)
Characteristics relevant to study population (Baseline PODSI [SD])	5.2 (1.1)	5.2 (1.2)

Primary Objective Result(s)

Total PODSI score

	Pimecrolimus cream (n=60)	**Vehicle cream (n=64)**	**Pimecrolimus cream vs Vehicle cream**
Baseline			
N	60	64	
Mean ± SD	5.2 ± 1.12	5.2 ± 1.20	
LS-Mean	5.2	5.2	
Average over visits 2,3 and 4			
N	60	63	
Mean ± SD	2.7± 1.44	3.5 ± 1.74	
LS-Mean	2.6	3.5	
Difference pimecrolimus vs vehicle			0.8
LS mean difference [1]			0.9
95% CI [1]			(0.4, 1.4)
P-value [1]			0.0011

[
[1] Between-group comparison. Least squares mean difference (Pimecrolimus – Vehicle), 95% confidence interval, and treatment p-value from an ANCOVA with baseline measurement as the covariate and treatment as the factor.

Secondary Objective Result(s)

Time to disease recurrence

Pimecrolimus cream (n=60)	Vehicle cream (n= 64)	Pimecrolimus cream vs vehicle cream p-value
could not be determined	106 days	p=0.1

Time to response (median time to response)

Pimecrolimus cream (n=60)	Vehicle cream (n= 64)	Pimecrolimus cream vs vehicle cream p-value
14 days	28 days	p=0.01

Responder rates (Response: Decrease in PODSI by >= 50% of the baseline value)

	Pimecrolimus cream (n=60) n (%)	Vehicle cream (n= 64) n (%)	Pimecrolimus cream vs vehicle cream % p-value
Visit			
Day 8	24 (40.0)	7 (10.9)	29.1 < .0001
Day 15	32 (53.3)	16 (25.0)	28.3 0.0008
Day 29	39 (65.0)	38 (59.4)	5.6 0.5177

Patients´quality of life (DLQI: Dermatology Life Quality Index)

	Pimecrolimus cream Mean (SD)	Vehicle cream Mean (SD)	Pimecrolimus cream vs vehicle cream Diff. (LS-Mean) p-value
Visit			
Baseline Day 1	8.8 (5.49) [n=60]	10.2 (7.29) [n=64]	1.4 (0.0)
Day 8	4.8 (5.7) [n=59]	8.1 (6.92) [n=59]	3.3 (2.6) 0.0028
Day 15	4.1 (4.44) [n=59]	5.7 (6.4) [n=58]	1.7 (1.3) 0.1286
Day 29	3.5 (4.54) [n=58]	4.5 (6.48) [n=56]	1.0 (0.8) 0.3975

Patients´subjective perception of disease severity (VAS)

	Pimecrolimus cream Mean (SD)	Vehicle cream Mean (SD)	Pimecrolimus cream vs vehicle cream Diff. (LS-Mean) p-value
Visit			
Baseline Day 1	64.4 (23.33) [n=60]	69.1 (23.51) [n=64]	4.7 (0.0)
Day 8	43.0 (23.52) [n=59]	57.4 (26.13) [n=59]	14.4 (11.8) 0.0008
Day 15	38.7 (28.15) [n=59]	46.2 (26.45) [n=58]	7.5 (6.3) 0.1883
Day 29	32.2 (27.72) [n=58]	36.6 (29.83) [n=56]	4.4 (3.8) 0.4971

Safety Results

Adverse Events by System Organ Class

	Pimecrolimus cream 60	Vehicle cream 64
Patients studied		
Randomized patients	60	64
Patients with AE	6 (10.0)	7 (10.9)
Patients with AEs by primary system organ class		
Respiratory, thoracic and mediastinal disorders	2 (3.3)	5 (7.8)
Nervous system disorders	17 (28.3)	19 (29.7)
Gastrointestinal disorders	5 (8.3)	10 (15.6)
Skin and subcutaneous tissue disorders	5 (8.3)	10 (15.6)
Infections and infestations	13 (21.7)	22 (34.4)

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

	Pimecrolimus cream n (% of patients))	Vehicle cream n (% of patients)
Abdominal Pain Upper	3 (5.0)	2 (3.1)
Diarrhoea	0 (0.0)	3 (4.7)
Gastroenteritis	1 (1.7)	2 (3.1)
Herpes Simplex	3 (5.0)	3 (4.7)
Nasopharyngitis	8 (13.3)	15 (23.4)
Back Pain	2 (3.3)	4 (6.3)
Burning Sensation	2 (3.3)	1 (1.6)
Cough	1 (1.7)	2 (3.1)
Erythema	2 (3.3)	3 (4.7)
Pruritus	2 (3.3)	3 (4.7)

Serious Adverse Events and Deaths

	Pimecrolimus	Vehicle
No. (%) of subjects studied	60	64
No. (%) of subjects with AE(s)	32 (53.3)	45 (70.3)
Number (%) of subjects with serious or other significant events	n (%)	n (%)
Death	0	0
SAE(s)	2 (3.3) *	3 (4.7)**
Discontinued due to SAE(s)	0	2 (3.1)***

*1 Carcinoma in situ of the cervix, 1 syncope/vascular encephalopathy

**1 Exacerbation perioral dermatitis, 1 Hyperglobulinemia, 1 Contact dermatitis

***1 Exacerbation perioral dermatitis, 1 Contact dermatitis

Other Relevant Findings

None

Date of Clinical Trial Report

21 Jun 2007

Date Inclusion on Novartis Clinical Trial Results Database

31-July-07

Date of Latest Update

27 July 2007