Sponsor
Novartis

Generic Drug Name
Pimecrolimus cream 1%

Therapeutic Area of Trial
Atopic Dermatitis (AD)

Approved Indication

U.K. indication:

- Treatment of patients aged 2 years and over with mild or moderate atopic dermatitis where treatment with topical corticosteroids is either inadvisable or not possible. This may include:
  - Intolerance to topical corticosteroids
  - Lack of effect of topical corticosteroids
  - Use on the face and neck where prolonged intermittent treatment with topical corticosteroids may be inappropriate

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
CASM981CGB02

Title
A 4-week, randomized, multicenter, parallel-group, placebo-controlled study to investigate the effect of pimecrolimus cream 1% on the quality of life (QoL) of patients with moderate facial atopic dermatitis (AD), in whom previous treatment, including appropriate use of topical corticosteroids (TCS), has been unsatisfactory.

Phase of Development
Phase IV

Study Start/End Dates
01-Mar-2005 to 24-Jan-2006

Study Design/Methodology
Multicenter, double-blind, parallel-group study to assess the effect of pimecrolimus cream 1% vs. vehicle on the QoL of patients with moderate AD, predominantly of the face and in whom previous treatment, including appropriate use of TCS, has been unsatisfactory. Patients within 3

days of a deterioration in symptoms necessitating further treatment and a pruritus score ≥ 2 (scale 0-3) were randomized 1:1 to 4 weeks of pimecrolimus cream 1% b.i.d. or corresponding vehicle on the face until satisfactory clearance. Study drug could be re-initiated at the first signs and symptoms of AD as required. The rest of the body was treated with study drug as appropriate.

Centres

20 centres in the United Kingdom

Publication

Ongoing

Objectives

Primary objective(s)

To assess the effect of pimecrolimus cream 1% used on the face (b.i.d) for 4 weeks in patients with moderate facial AD on quality of life.

Secondary objective(s)

To determine the effect after 4 weeks of pimecrolimus cream 1% in patients with moderate facial AD on

- Signs of AD - IGA
- Signs of AD – patient assessment
- Facial pruritus (itch) – patient assessment
- Patient treatment satisfaction
- Time to clearance of AD

In addition, drug utilization, safety and tolerability were assessed at the end of 4 weeks.

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

Pimecrolimus cream 1% was supplied in 50g tubes and applied topically b.i.d. to lesional areas of AD on the face, neck & body

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

Vehicle cream to match pimecrolimus cream 1% was supplied in 50g tubes and applied topically b.i.d. to lesional areas of AD on the face, neck & body

Criteria for Evaluation

Primary variables

- Change from baseline in the Quality of Life Index for Atopic Dermatitis (QoLIAD) score at Week 4
- The QoLIAD
  - is a 25 item questionnaire answered ‘true’ (score=1) or ‘not true’ (score=0)
  - has a theoretical scale range from 0 to 25
  - is expressed as a percentage of the maximum possible score of 25. The higher the QoLIAD score, the greater the impairment of quality of life

Secondary variables

- Investigator’s Global Assessment (IGA) score (0=clear, 5=very severe) (face only)
- Patient’s daily Global Assessment of efficacy score (0=clear, 5=worst ever) (face only)
- Patient’s daily pruritus severity assessment score (0=absent, 3=severe) (face only)
- Patient satisfaction with treatment – measured by questionnaire

- Time from baseline to clearance of AD (The clearance of AD was defined from the IGA as a score of 0 or 1 (clear or almost clear)
- Drug utilization was measured by the investigator by comparing the number of tubes of study drug dispensed at the outset of the study with the number returned by the patient at the study end.

Safety and tolerability

Frequency of adverse events including local skin reactions together with overall tolerability was assessed by the investigator and patient (scale 1=very good, 5=very poor).

Statistical Methods

Primary objective

The change from baseline in QoLIAD score was analysed using an analysis of covariance model with centre and treatment group as factors and baseline QoLIAD as a covariate. The null hypothesis tested was that the effects of pimecrolimus and vehicle in improving QoLIAD score (change from baseline at 4 weeks) are the same versus the alternate hypothesis that they are not. The null hypothesis will be rejected at an alpha level of 0.05

Secondary objectives

IGA: Between treatment comparisons were made using the Wilcoxon 2-sample test.

Patient's Global Assessment (face only) and Pruritus Severity Assessment (face only): Scores at each evaluation were summed to give an aggregate total efficacy score. Between treatment comparisons were made using the Wilcoxon 2-sample test. Summary statistics will also be provided to show the time-course of global assessments.

Time from baseline to clearance of AD: The data was described by cumulative Kaplan-Meier estimates. Between group comparisons were made using the log-rank test.

Drug utilization: The proportions of tubes that were full, partially used or empty were compared between the two groups using a Chi-squared test for homogeneity.

Safety

The data collected will be presented in listings, summary tables and graphs. All analyses were performed on the safety population.

Adverse Events

Adverse events were summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event.

Overall tolerability as assessed by the investigator and subject: The proportions in each category and summary statistic were listed. Between treatment comparisons were made using the Wilcoxon 2-sample test.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males and females aged 18 years or older
- Active moderate facial AD at baseline (Facial IGA score of 3), within 3 days of a deterio-

ration in symptoms that necessitates further treatment
- Pruritus score of 2 or above at baseline
- Patients in whom further use of topical corticosteroids (TCS) is clinically inappropriate due to:
  - burning, stinging, allergic reaction or other adverse event that prevents the patient from using topical corticosteroids to successfully treat an AD flare on the face
  - presence of rosacea, telangiectasia, skin atrophy or glaucoma as a result of topical corticosteroid usage on the face
  - presence of AD on the eyelids

Or patients for whom previous treatment has been unsatisfactory and who would prefer to try an alternative treatment option.
- Patients who have been informed of the study procedures and have signed the informed consent form approved for the study.

Exclusion criteria

- At baseline and throughout the study, females of childbearing potential:
  - Who are pregnant or breast-feeding
  - Who are menstruating, capable of becoming pregnant, and not practicing a medically approved method of contraception during and up to at least 4 weeks after the end of study treatment. A negative pregnancy test (urine) for all females of childbearing potential is required at the screening visit. 'Medically approved' contraception may include abstinence at the discretion of the investigator
- At baseline and throughout the study, all patients:
  - Who have received phototherapy (e.g. UVB, UVA) or systemic therapy (e.g. immunosuppressants, cytostatics) known or suspected to have an effect on AD within 1 month of Visit 1 (baseline)
  - Who have received systemic corticosteroids (e.g. oral, intravenous, intra-articular, rectal) within 1 month of Visit 1. Patients on a stable maintenance dose of inhaled corticosteroids may participate
  - Who have a known or suspected contact allergic dermatitis
  - Who have received systemic antibiotics within 2 weeks prior to Visit 1
  - Who have used oral or topical antihistamines for the treatment of pruritus within 2 weeks prior to visit 1
  - Who have applied topical therapy (e.g. tar, topical corticosteroids, pimecrolimus or tacrolimus within 2 weeks prior to screening
  - Who have used potent or very potent TCS within 4 weeks prior to Visit 1.
  - Who are immunocompromised (e.g. lymphoma, HIV infection/AIDS, Wiskott-Aldrich Syndrome) or have a history of malignant disease
  - Who have a history of poor or no clinical response, or hypersensitivity to topical pimecrolimus
  - Who have concurrent skin disease (e.g. acne) of such severity in the study area that it could interfere with the evaluation.
  - Who have active bacterial (e.g. impetigo), viral (e.g. chicken pox, herpes simplex) or fungal infections (e.g. tinea corporis, intertriginosa)
  - Who have received any investigational drugs within 8 weeks of visit 1, or plan to use any other investigational drugs during the course of this study
  - Who, in the opinion of the investigator, are known to be unreliable, who are non-compliant with medical treatment, or are known to miss appointments
  - Who have abuse problems, mental dysfunction or other factors limiting their ability to cooperate fully in study-related procedures
  - Who have any condition or prior/present treatment that, in the opinion of the investigator, should render them ineligible for the study

Number of Subjects

	Pimecrolimus cream	Vehicle
Screened N	44	46
Randomised n (%)	44 (100%)	46 (100%)
Exposed n (%) (safety population)	44 (100%)	46 (100%)
Intention to treat (ITT) population n (%)	40 (90.9%)	42 (91.3%)
Completed n (%)	37 (84.1%)	30 (65.2%)
Withdrawn n (%)	7 (15.9%)	16 (34.8%)
Withdrawn due to adverse events n (%)	1 (2.3%)	4 (8.7%)
Withdrawn due to lack of efficacy n (%)	4 (9.1%)	8 (17.4%)
Withdrawn due to protocol violation n (%)	1 (2.3%)	2 (4.3%)
Withdrawn for other reasons n (%)	1 (2.3%)	2 (4.3%)

Demographic and Background Characteristics

ITT population	**Pimecrolimus cream (n=40)**	**Vehicle (n=42)**
Male n (%)	16 (40.0%)	19 (45.2%)
Female n (%)	24 (60.0%)	23 (54.8%)
Mean age, years (SD)	49 (± 21.4)	48 (± 17.1)
Race White n (%) Black n (%) Oriental n (%) Other n (%)	 39 (97.5%) 1 (2.5%) 0 (0.0%) 0 (0.0%)	 41 (97.6%) 1 (2.4%) 0 (0.0%) 0 (0.0%)
AD severity score – subject assessment – mean (SD)	3.0 (± 0.58)	3.2 (± 0.48)
Pruritus score – subject assessment – mean (SD)	2.1 (± 0.46)	2.1 (± 0.46)

Primary Objective Result(s)

Percent quality of life score (QoLIAD)

ITT population	**Pimecrolimus cream (n=40)**	**vehicle (n=42)**
Baseline		
Mean ± SD	33.9 ± 30.85	29.7 ± 26.16
Median	26.0	24.0
Range	0-96	0-100
Week 4 (LOCF)		
Mean ± SD	16.7 ± 28.21	22.9 ± 29.54
Median	4.0	10.0
Range	0-100	0-100
Change from baseline		
Mean ± SD	-17.2 ± 23.99	-6.9 ± 17.79
Median	-10.0	-2.0
Range	-92-12	-62-28

Treatment difference (adjusted means, pimecrolimus minus vehicle)	-8.85
95% confidence interval	-17.68, -0.02
P value	P=0.0495

Secondary Objective Result(s)

Investigator Global Assessment (IGA)

ITT population	**Pimecrolimus cream (n=40)**	**vehicle (n=42)**
Baseline		
Mean ± SD	3.0 ± 0.00	3.0 ± 0.22
Median	3.0	3.0
Range	3-3	3-4
Week 4		
Mean ± SD	1.6 ± 1.15	2.3 ± 1.38
Median	1.0	2.0
Range	0-4	0-5

Between group comparisons (Wilcoxon 2-sample tests)	
Baseline p-value	P=0.1703
Day 28 p-value	P=0.0139

Patient Assessment (aggregate scores*)

Eczema score

	Pimecrolimus cream (n=40)	**vehicle (n=37)**
Mean ± SD	41.0 ± 23.61	38.7 ± 26.08
Median	41.3	33.5
Range	6-85	3-89

*Aggregate scores for eczema were derived from daily diary recordings and are the AUC of the scores. Eczema scored on 6-point scale from 0=clear to 5=worst ever eczema.

Between group comparisons (Wilcoxon 2-sample tests)	
p-value	P=0.5889

Patient Assessment Facial pruritus (itch) score (aggregate score*)

	Pimecrolimus cream (n=40)	**vehicle (n=38)**
Mean ± SD	27.0 ± 18.64	26.5 ± 20.63
Median	26.0	22.0
Range	2-84	1-84

*Aggregate scores for pruritus were derived from daily diary recordings and are the AUC of the scores. Pruritus scored on 4-point scale from 0=none to 3=severe.

Between group comparisons (Wilcoxon 2-sample tests)	
p-value	P=0.7003

Patient treatment satisfaction

ITT population	**Pimecrolimus cream (n=40) n (%)**	**vehicle(n=42) n (%)**	**P-value**
Expectations of treatment			0.4044
Far above expectations	4 (10.0%)	3 (7.7%)	
Above expectations	11 (27.5%)	6 (15.4%)	
Met expectations	10 (25.0%)	8 (20.5%)	
Below expectations	12 (30.0%)	13 (33.3%)	
Far below expectations	3 (7.5%)	8 (20.5%)	
Patients Global Satisfaction assessment			0.2024
Extremely satisfied	8 (20.0%)	6 (15.4%)	
Satisfied	15 (37.5%)	7 (17.9%)	
Neither satisfied or dissatisfied	8 (20.0%)	13 (33.3%)	
Dissatisfied	8 (20.0%)	8 (20.5%)	
Extremely dissatisfied	1 (2.5%)	4 (10.3%)	
Previous treatment for atopic dermatitis?			0.33223
Yes	34 (85.0%)	29 (74.4%)	
No	6 (15.0%)	9 (23.1%)	
Overall preference			0.0596
Definitely prefer current treatment	15 (37.5%)	8 (20.5%)	
Slight preference for current treatment	5 (12.5%)	3 (7.7%)	
No preference	9 (22.5%)	9 (23.1%)	
Slight preference for previous treatment	6 (15.0%)	4 (10.3%)	
Definitely prefer previous treatment	2 (5.0%)	12 (30.8%)	
Willingness to use medication again			0.0761
Definitely want to use same medication	19 (47.5%)	12 (30.8%)	
Might want to use same medication	6 (15.0%)	7 (17.9%)	
I am not sure	8 (20.0%)	5 (12.8%)	
Might not want to use same medication	4 (10.0%)	2 (5.1%)	
Definitely not want to use same medication	3 (7.5%)	12 (30.8%)	
Would you recommend medication?			0.0146
Yes	30 (75.0%)	18 (46.2%)	
No	10 (25.0%)	20 (51.3%)	

Time to clearance of AD

Days to first clearance (IGA score 0 or 1) (ITT population)	**Pimecrolimus cream n=40**	**vehicle n=42**	**P-value (log rank test|)**
25th percentile	3 (2,4)	4 (2,8)	0.1058
Median	5 (4,7)	11 (5,)	
75th percentile	19 (5,)	(15,5)	

Wilcoxon test P value=0.1058

Drug utilization

ITT population	**Pimecrolimus cream n=40 n (%)**	**vehicle n=42 n (%)**	**P-value**
Medication returned			1.0000
Yes	39 (97.5%)	39 (95.1%)	
No	1 (2.5%)	2 (4.9%)	
Facial tube status			0.3737
Approximately full	1 (2.5%)	4 (9.8%)	
Approximately ¾ full	17 (42.5%)	19 (46.3%)	
About half full	13 (32.5%)	7 (17.1%)	
About quarter full	3 (7.5%)	6 (14.6%)	

Empty	5 (12.5%)	3 (7.3%)

Safety Results

Overall tolerability: proportions

ITT population	**Pimecrolimus cream n=40**	**vehicle n=42**	**P-value**
Investigator overall tolerability – n (%)			0.0426
Very good	23 (57.5%)	13 (31.7%)	
Good	11 (27.5%)	13 (31.7%)	
Moderate	4 (10.0%)	5 (12.2%)	
Poor	2 (5.0%)	3 (7.3%)	
Very poor	0 (0.0%)	6 (14.6%)	
Subject overall tolerability – n (%)			0.0289
Very good	23 (57.5%)	12 (29.3%)	
Good	9 (22.2%)	14 (34.1%)	
Moderate	5 (12.5%)	3 (7.3%)	
Poor	3 (7.5%)	7 (17.1%)	
Very poor	0 (0.0%)	4 (9.8%)	

Adverse Events by System Organ Class

Number (%) of patients with AEs, by system organ class and preferred term

	Pimecrolimus cream n (%)	vehicle n (%)
Patients studied		
Randomized patients	44	46
Patients with any AE n (%)	19 (43.2%)	17 (37.0%)
Eye disorders		
Eye irritation	1 (2.3%)	0
Eye pain	0	1 (2.2%)
Eyelid disorder	0	1 (3.4%)
Eyelid irritation	0	1 (2.2%)
Eyelid oedema	0	1 (2.2%)
Gastrointestinal disorders		
Dyspepsia	0	1 (2.2%)
Lip swelling	1 (2.3%)	0
Rectal haemorrhage	1 (2.3%)	0
General disorders and administration site conditions		
Application site irritation	2 (4.5%)	0
Application site pain	1 (2.3%)	0
Chest pain	1 (2.3%)	0
Facial pain	1 (2.3%)	1 (2.2%)
Fatigue	0	1 (2.2%)
Gravitational oedema	1 (2.3%)	0
No adverse effect	0	1 (2.2%)
Immune system disorders		
Hypersensitivity	0	1 (2.2%)
Seasonal allergy	0	1 (2.2%)
Infections and infestations		
Eczema infected	0	2 (4.3%)
Herpes simplex	1 (2.3%)	1 (2.2%)
Influenza	0	1 (2.2%)
Lower respiratory tract infection	1 (2.3%)	1 (2.2%)
Nasopharyngitis	0	1 (2.2%)
Pneumonia	1 (2.3%)	0
Injury, poisonings and procedural complications		
Contusion	0	1 (2.2%)
Joint injury	1 (2.3%)	0
Muscle strain	1 (2.3%)	0
Musculoskeletal and connective tissue disorders		
Joint swelling	1 (2.3%)	0
Musculoskeletal chest pain	1 (2.3%)	0
Myalgia	0	1 (2.2%)
Plantar fasciitis	1 (2.3%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Seborrhoeic keratosis	1 (2.3%)	0
Nervous system disorders		
Burning sensation	2 (4.5%)	1 (2.2%)
Dizziness	2 (4.5%)	0
Headache	1 (2.3%)	2 (4.3%)
Migraine	0	1 (2.2%)
Psychiatric disorders		
Bipolar disorder	1 (2.3%)	0

Insomnia	0	1 (2.2%)
Reproductive system and breast disorders		
Menstruation irregular	0	1 (2.2%)
Prostatitis	0	1 (2.2%)
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	1 (2.3%)	0
Pleuritic pain	1 (2.3%)	0
Sinus congestion	1 (2.3%)	0
Skin and subcutaneous tissue disorders		
Eczema	0	1 (2.2%)
Pruritus	0	1 (2.2%)
Psoriasis	1 (2.3%)	0
Rash erythematous	0	1 (2.2%)
Rosacea	1 (2.3%)	0
Skin burning sensation	1 (2.3%)	0
Vascular disorders		
Hypertension	1 (2.3%)	0

Drug-related AEs by system organ class

Safety population	**Pimecrolimus cream (n=44)**	**vehicle (n=46)**
Eye disorders	1 (2.3%)	4 (8.7%)
General disorders & administration site conditions	4 (9.1%)	1 (2.2%)
Nervous system disorders	1 (2.3%)	2 (4.3%)
Skin and subcutaneous tissue disorders	1 (2.3%)	2 (4.3%)

Most frequently reported AEs overall by preferred Term (≥3% for any group)

Safety population	**Pimecrolimus cream (n=44)**	**vehicle (n=46)**
Application site irritation	2 (4.5%)	0 (0.0%)
Burning sensation	2 (4.5%)	1 (2.2%)
Dizziness	2 (4.5%)	0 (0.0%)
Eczema infected	0 (0.0%)	2 (4.3%)
Headache	1 (2.3%)	2 (4.3%)

Serious Adverse Events and Deaths

Safety population	**Pimecrolimus cream n (%)**	**vehicle n (%)**
Total no. of patients	44	46
Death	0 (0.0)	0 (0.0)
SAE(s)	1 (2.3%)	0 (0.0)
Clinically significant AEs	2 (4.5%)	6 (13.0%)
Discontinued due to SAE(s)	0 (0.0)	0 (0.0)
Discontinued due to clinically significant AEs	1 (2.3%)	5 (10.9%)

One patient in the pimecrolimus group had pneumonia.

Other Relevant Findings

N/A

Date of Clinical Trial Report

Ongoing

Date Inclusion on Novartis Clinical Trial Results Database **20-Jun-2007**
Date of Latest Update **07-Jun-2007**