Sponsor–Novartis	**Web Page/Link to Prescribing/Label Information–** http://www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name–Pimecrolimus	
Therapeutic Area of Trial– Atopic dermatitis	
Approved Indication–Atopic dermatitis	
Study Number–ASM981 C2316	
Title– A 26-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the incidence of atopic dermatitis flares when pimecrolimus) cream 1% is used at the first signs and/or symptoms of atopic dermatitis and its safety and tolerability in adults 18 years of age and older	
Phase of Development–IV	
Study Start/End dates– 29-Oct-2003 through 24-Sep-2004	
Study Design/Methodology– This was a multicenter, randomized, double-blind, parallel-group, vehicle-controlled comparative study. Skin care with emollients was recommended for all patients. Pimecrolimus or matching vehicle cream was started at the onset of first signs and/or symptoms of AD. In the event of worsening of AD after at least 3 days of study treatment use and after investigator confirmation of flare, a medium potency TCS, or alternative TCS for sensitive body areas, was allowed. The vehicle cream (control) group represented the current standard of care for AD, i.e. emollients and reactive use of medium potency TCS for disease flares.	
Centres– Sixty-three centers in 7 countries recruited patients (number of centers in brackets): Canada (5), Germany (25), Spain (4), Finland (4), France (7), Great Britain (5) and the United States (13).	
Publication– Publications are ongoing.	
Objectives– *Primary outcome/efficacy objective(s)–* • To investigate the efficacy of pimecrolimus cream 1% administered b.i.d. compared to vehicle cream administered b.i.d. in preventing flares (as defined by reducing resultant reactive topical corticosteroid use) in AD over a 26-week period in adults 18 years of age and older. *Secondary outcome/efficacy objective(s)–* • To investigate the efficacy of pimecrolimus cream 1% administered b.i.d. compared to pimecrolimus vehicle cream administered b.i.d. in preventing flares in AD in adults, as primarily demonstrated by ranking patients with regard to the number of flares they experience while participating in the 26-week study • to evaluate the safety of pimecrolimus-based treatment in AD.	
Test Product, Dose, and Mode of Administration– Pimecrolimus cream 1% was supplied in 50g tubes, and applied as a thin film b.i.d. to affected areas until symptoms resolved or TCS was required.	
Reference Product(s), Dose(s), and Mode(s) of Administration– Matching vehicle cream was supplied in 50g tubes, and applied as a thin film b.i.d. to affected areas until symptoms resolved or TCS was required.	
Criteria for Evaluation– *Primary efficacy:* Flare-free days reflecting the number of days on study without TCS use (per patient diary). *Secondary efficacy:* • Flares per patient with patients ranked according to the number of the flares they experienced during the trial • Time to first flare and the duration of TCS treatment required per flare were also assessed as secondary efficacy parameters. Since there were a sufficient number of flares after the initial one, the time to subsequent flares was also assessed. • Other secondary efficacy assessments were Investigator's global assessment (IGA) score and	

patients pruritus severity score reported via a Daily Diary.

Safety/tolerability:. Safety assessments consisted of monitoring and recording all adverse events (AEs), serious adverse events (SAEs) and pregnancies, vital signs and area of disease involvement. Laboratory evaluations and electrocardiograms were not required in this study.

Pharmacology: not applicable

Statistical Methods–Demographic and disease characteristics, and study medication exposure were summarized for all randomized, all intent-to-treat (ITT), and all Daily Diary ITT patients, as applicable. Summary statistics are provided for continuous variables, and frequency counts are provided for discrete variables. Efficacy analyses were performed for the Daily Diary ITT or the ITT populations, as appropriate. The primary efficacy variable (i.e., number of days without TCS use) and the main secondary efficacy variables (i.e., ranking patients by number of flares they had [also known as 'ranked flares']) were analyzed using the van Elteren test stratified by center. The other secondary efficacy variables were analyzed using the van Elteren test, statistical life-table methods, the Wilcoxon rank sum test, cox regression and the analysis of variance (ANOVA). All statistical tests are two-sided using a level of significance of 0.05. Descriptive statistics were used for all safety variables for the safety population. No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics–. Included were adults, 18 years of age or older, with a history of mild to moderate AD (Investigator's Global Assessment score of 2 or 3) requiring treatment with topical corticosteroid (TCS), pimecrolimus or tacrolimus at least twice in the 6 months preceding randomization, with at least one event occurring within 3 months of randomization. Patients were required to have an IGA score of 0 (clear) or 1 (almost clear) before randomization. Patients were excluded for the use of systemic corticosteroids (SCS), immunosuppressants, cytostatics, or phototherapy within 1 month of Visit 1, topical tacrolimus ointment within four weeks, systemic antibiotics within 2 weeks, topical therapy other than topical calcineurin inhibitors (e.g. corticosteroids, tar) known or suspected to have an effect on AD within 7 days of Visit 1, investigational drugs within 8 weeks. Patients having a history of malignancy, or inadequate response to tacrolimus or pimecrolimus, and those that had immunocompromised status, concurrent skin disease that could interfere with study evaluation, active bacterial, viral, or fungal infections, head lice or scabies, or known hypersensitivity to any ingredient of the study medications were also excluded.

Number of Subjects	Pimecrolimus cream 1% n (%)	Vehicle n (%)
Planned	250	250
Randomized	277	266
Completed	234 (84.5)	209 (78.6)
Withdrawn	43 (15.5)	57 (21.4)
Treated	264 (95.3)	256 (96.2)
Withdrawn due to adverse events	1 (0.4)	6 (2.3)
Withdrawn due to lack of efficacy	12 (4.3)	19 (7.1)
Withdrawn for other reasons	30 (10.9)	32 (12.1)
Demographic and Background Characteristics (Randomized population)		
N	277	266
Females : males	185:92	189:77
Mean age, years (SD)	35.4 (14.28)	34.8 (12.94)
Mean weight, kg (SD)	n=276 72.6 (17.03)	n=265 70.2 (15.34)
Race		
White n (%)	246 (88.8)	232 (87.2)
Black n (%)	11 (4.0)	11 (4.1)
Asian n (%)	9 (3.2)	11 (4.1)
Other n (%)	11 (4.0)	12 (4.5)

Mean height, cm (SD)	n=275 169.9 (9.62)	n=265 168.4 (9.36)
Primary Efficacy Result(s)– Daily Diary ITT population		
Number of days on study without topical corticosteroid use	Pimecrolimus cream 1% (N=265)	Vehicle cream (N=257)
Mean days (SD) p-value <0.0001	152.0 (43.99)	138.7 (53.15)
Secondary efficacy result(s)–intent to treat population **Number of flares as determined by the investigator**		
Actual and imputed number of flares after ranking Mean rank n (SD) p-value=0.0004	Pimecrolimus cream 1% 243.2 (142.98)	Vehicle cream 287.6 (150.68)
Actual and imputed number of flares Mean n (SD) p-value=0.0014	0.97 (1.509)	1.39 (1.722)
Actual number of flares n (%)		
0	147 (54.6)	110 (42.3)
1	69 (25.7)	76 (29.2)
2	28 (10.4)	34 (13.1)
3	13 (4.8)	13 (5.0)
4	3 (1.1)	14 (5.4)
>4	9 (3.3)	13 (5.0)

Time to occurrence of first flare and recurrent event analysis of time to flare (ITT population)

	Hazard ratio	95% CI for hazard ratio	Wald χ^2 p-value
Cox regression for time to first flare [1]			
Treatment (pimecrolimus 1% versus vehicle)	0.593	(0.478 , 0.735)	<0.0001
Recurrent event analysis [2]			
Time to second flare			
Treatment (pimecrolimus 1% versus vehicle)	0.933	(0.628 , 1.387)	0.7327
Time to third flare			
Treatment (pimecrolimus 1% versus vehicle)	0.823	(0.440 , 1.541)	0.5425

[1] The model included treatment, 'standardized' age, and the last IGA score (dichotomized as clear vs not clear) prior to first use of study medication or topical corticosteroids whichever was earlier as covariates. Pooled center was removed from the model because the model was overspecified.

[2] Results of conditional proportional hazards model for time to flare (see 'gap time' model of Prentice, Williams, Peterson (1981)). Model included same variables as covariates as for the first flare model

A hazard ratio less than 1 favors pimecrolimus cream.
Only including flares that started not later 189 days after randomization.

Number of days on topical corticosteroids per flare (ITT population)

	Pimecrolimus cream 1% (N=269)	Vehicle cream (N=260)
n	110	137
Mean	9.8	8.8
SD	8.22	8.70
Minimum	1	1
Median	7.3	6.0
Maximum	58	71
p-value [1]	0.2517	

[1] p-value of van Elteren test stratified by pooled center

n = number of patients with a confirmed flare with topical corticosteroid use which resolved before RDay 190 or discontinuation, whichever came first. (RDay = days after randomization).

Investigator's global assessment at time of first and second flare (ITT population, patients with respective number of flares)

	Number (%) of patients	
	At time of first flare	At time of second flare
Pimecrolimus cream 1% - number of patients with respective flare [1]	121	53
0 (Clear)	1 (0.9)	0 (0.0)
1 (Almost clear)	17 (15.9)	8 (18.6)
2 (Mild disease)	34 (31.8)	11 (25.6)
3 (Moderate disease)	45 (42.1)	22 (51.2)
4 (Severe disease)	8 (7.5)	1 (2.3)
5 (Very severe disease)	2 (1.9)	1 (2.3)
Total [2]	107 (100.0)	43 (100.0)
Vehicle cream - number of patients with respective flare [1]	149	74
0 (Clear)	0 (0.0)	0 (0.0)
1 (Almost clear)	12 (8.8)	4 (6.8)
2 (Mild disease)	37 (27.2)	11 (18.6)
3 (Moderate disease)	77 (56.6)	34 (57.6)
4 (Severe disease)	9 (6.6)	10 (16.9)
5 (Very severe disease)	1 (0.7)	0 (0.0)
Total [2]	136 (100.0)	59 (100.0)
p-value [3]	0.0772	0.0129

[1] Not including early discontinuations because of lack of efficacy which were otherwise counted as flares if the conditions described in Section 6 were fulfilled.

[2] Only including patients with a non-missing IGA score at the respective flare.

[3] exact p-value of Wilcoxon rank sum test

Percentages and Wilcoxon test are based on patients with non-missing IGA score at respective flare.

Only including flares that started not later than 189 days after randomization.

Average of pruritus severity scores recorded on consecutive days with study medication prior to topical corticosteroid use for first/second flare (ITT population, patients with respective number of flares or more)

	Pimecrolimus cream 1% (N=269)		Vehicle cream (N=260)
Prior to topical corticosteroid use for first flare			
Number of patients with 1st flare	121		149
n	103		125
Mean	1.63		1.74
SD	0.686		0.676
Minimum	0.0		0.0
Median	1.62		1.80
Maximum	3.0		3.0
p-value [1]		0.3155	
Prior to topical corticosteroid use for second flare			
Number of patients with 2nd flare	53		74
n	44		62
Mean	1.51		1.63
SD	0.552		0.704
Minimum	0.1		0.0
Median	1.48		1.68
Maximum	3.0		3.0
p-value [1]		0.3682	

[1] p-value of Wilcoxon rank-sum test

n = number of patients included in the analysis. n may be smaller than the number of patients with 1st/2nd flare because patients may not have used study medication prior to topical corticosteroid use for 1st/2nd flare or may not have recorded pruritus severity scores on respective days with study medication.

Only including flares that started not later than 189 days after randomization.

Pruritus severity score: 0=none/absent, 1=mild, 2=moderate, 3=severe.

Safety Results

Patients with Adverse Events and Adverse Events by System Organ Class

Patients n (%) studied	**Pimecrolimus cream 1%**	**Vehicle cream**
Total no. of patients	264 (100.0)	254 (100.0)
Total no. with AEs	180 (68.2)	158 (62.2)
Significant events		
AEs leading to premature discontinuation	1 (0.4)	6 (2.4)
Dose adjustment/interruption due to AE	3 (1.1)	4 (1.6)
System organ class affected		
Infections and infestations	119 (45.1)	104 (40.9)
Nervous system disorders	59 (22.3)	41 (16.1)
Gastrointestinal disorders	33 (12.5)	37 (14.6)
General disorders and administration site Conditions	28 (10.6)	15 (5.9)
Respiratory, thoracic and mediastinal Disorders	27 (10.2)	20 (7.9)
Musculoskeletal and connective tissue disorders	18 (6.8)	18 (7.1)
Skin and subcutaneous tissue disorders	17 (6.4)	11 (4.3)
Immune system disorders	16 (6.1)	10 (3.9)
Injury, poisoning and procedural complications	10 (3.8)	10 (3.9)
Eye disorders	9 (3.4)	9 (3.5)
Reproductive system and breast disorders	8 (3.0)	11 (4.3)
Psychiatric disorders	7 (2.7)	15 (5.9)
Ear and labyrinth disorders	6 (2.3)	4 (1.6)

10 Most Frequently Reported AEs Overall by Preferred Term	**Pimecrolimus cream 1% n (%)**	**Vehicle cream n (%)**
Nasopharyngitis	54 (20.5)	38 (15.0)
Headache	52 (19.7)	34 (13.4)
Influenza	17 (6.4)	17 (6.7)
Seasonal allergy	14 (5.3)	6 (2.4)
Application site burning	11 (4.2)	2 (0.8)
Rhinitis allergic	11 (4.2)	5 (2.0)
Asthma	9 (3.4)	3 (1.2)
Herpes simplex	9 (3.4)	12 (4.7)
Rhinitis	9 (3.4)	5 (2.0)
Back pain	8 (3.0)	7 (2.8)

Serious Adverse Events and Deaths

Patients studied	**Pimecrolimus cream 1%**	**Vehicle cream**
Total no. of patients with SAEs n (%)	5 (1.9)	7 (2.8)
Serious events		
Death	0 (0.0)	0 (0.0)
SAEs	5 (1.9)	7 (2.8)

Other Relevant Findings–

Date of Clinical Trial Report–	14-Jan-2005	
Date Inclusion on Registry–	Aug 2005	

Date of Latest Update–	Aug 2005	