Sponsor– NOVARTIS	**Web Page/Link to Prescribing/Label Information–** www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Pimecrolimus	
Therapeutic Area of Trial– Dermatology	
Approved Indication– Mild/moderate atopic dermatitis, >2 yr age	
Study Number– CASM981C1303	
Title–Confirmatory study in adult patients with atopic dermatitis	
Phase of Development– III	
Study Start/End dates– 15-Nov-2003 through 17-Nov-2004	
Study Design/Methodology– Multicenter, randomized, double-blind, parallel-group, vehicle-controlled study with a 26-week treatment phase to determine the efficacy, safety of pimecrolimus cream for long-term treatment of adult patients with atopic dermatitis	
Centres– 25 centers in Japan	
Publication– on-going	
Objectives– *Primary outcome/efficacy objective(s)–* To evaluate topical application of pimecrolimus cream compared to vehicle in reducing the number of flares in patients with atopic dermatitis *Secondary outcome/efficacy objective(s)–* To evaluate topical application of pimecrolimus cream compared to vehicle in preventing flares using 'Ranked Flare' and 'Time to first flare'. **Test Product, Dose, and Mode of Administration–** Pimecrolimus cream 1% or vehicle was applied to affected area twice a day. When eczema worsened to severe or very severe, topical corticosteroids and/or tacrolimus hydrate ointment were applied to affected area twice a day. After the remission of eczema by the treatment of topical corticosteroids and/or tacrolimus hydrate ointment, pimecrolimus cream 1% or vehicle was applied again. **Reference Product(s), Dose(s), and Mode(s) of Administration–** Vehicle was applied in the same manner as pimecrolimus.	
Criteria for Evaluation– *Primary efficacy:* Number of flares. 'Flare' was counted when all the three criteria as follows were fulfilled: - Severity of eczema was evaluated severe or very severe based on the definition of IGA (Investigators' Global assessment) score. - Patient applied topical corticosteroids or tacrolimus hydrate ointment within 3 days after the evaluation above. - More than 7 days had passed since the patient had applied topical corticosteroids or tacrolimus hydrate ointment during the last 'Flare'. To evaluate the number of flares, 'Flare rate' was defined as the primary efficacy variable. 'Flare rate' was defined as the total number of flares divided by the total number of days on study in each treatment group. *Secondary efficacy:* 'Ranked Flare' and 'Time to first flare' were calculated based on the 'Flare' evaluation. *Safety/tolerability:* Safety assessments consisted of monitoring and recording all adverse events and serious adverse events as well as regular monitoring of hematology, blood chemistry, and urine values, and physical examinations. *Other:* None	

Pharmacology: None

Statistical Methods–

Primary efficacy

'Flare rate' in pimecrolimus group was compared to that in vehicle group by permutation test. Significance was set at the 5% level.

Secondary efficacy

Cochran-Mantel-Haenszel test for Ranked flare was conducted to compare the number of flares between pimecrolimus group and vehicle group. Log rank test for Kaplan-Meier estimate of time to first flare was conducted.

Post-hoc analysis for efficacy

According to the results of primary efficacy and secondary efficacy as well as number of discontinued patients due to unsatisfactory therapeutic effect, all the analysis except primary efficacy showed the efficacy of pimecrolimus cream compared to vehicle. In this study, the number of flares could be under estimated if discontinuations for lack of treatment efficacy occurred. However, the primary efficacy analysis does not adjust for this negative bias caused by the extensive control group discontinuations. Therefore, this analysis is not adequate for this type of problem.

As post-hoc analysis, adjusted flare rate in pimecrolimus group was compared to that in vehicle group by permutation test. Adjusted flare rate was calculated by adding four flares and adjusting study duration to 183 days in all patients that discontinued due to lack of efficacy.

Safety

The incidence and the change of adverse effects and abnormal laboratory values were summarized and listed.

Study Population: Inclusion/Exclusion Criteria and Demographics–

Subjects aged 16 to <65 years with AD according to the diagnostic criteria of Japanese Dermatological Association affecting at least 5% total body surface area, with Investigator's Global Assessment score of ≥2 (i.e. at least mild disease and no restriction on severity).

Subjects were excluded if they had received phototherapy or systemic therapy (including corticosteroids or immunosuppressants) which could have affected AD within 4 weeks of the study, antibiotics, antivirals or antifungals within 2 weeks of the study, or topical therapy which could have affected their AD or systemic antiallergic drugs (sodium cromoglicate, tranilast or suplatast tosilate) within 7 days of the study. Also excluded were subjects with a history of malignant disease, with active skin infections or other systemic infections, or with other skin conditions that could have affected the evaluation of study treatment.

Number of Subjects	Pimecrolimus 1%	Vehicle
Planned N	80	80
Randomised n	86	87
Completed n (%)	80 (93.0)	66 (75.9)
Withdrawn n (%)	6 (7.0)	21 (24.1)
Included in the primary analysis n (%)	85 (98.8)	87 (100)
Withdrawn due to adverse events n (%)	2 (2.3)	5 (5.7)
Withdrawn due to lack of efficacy n (%)	1 (1.2)	10 (11.5)
Withdrawn for other reasons n (%)	3 (3.5)	6 (6.9)
Demographic and Background Characteristics		
N (ITT)	85	87
Females:males	54 : 31	53 : 34
Mean age, years (SD)	26.7 (7.8)	27.8 (7.8)
Mean weight, kg (SD)	56.0 (10.3)	57.3 (10.7)

Race		
White n (%)	0	0
Black n (%)	0	0
Asian n (%)	85 (100)	87 (100)
Other n (%)	0	0
Baseline IGA score (Baseline severity)		
2 (Mild)	21 (24.7)	23 (26.4)
3 (Moderate)	58 (68.2)	58 (66.7)
4 (Severe)	6 (7.1)	6 (6.9)
Primary Efficacy Result(s)– Full analysis set		
Number of Flare	Pimecrolimus 1%	Vehicle
Total number of flares (times)	122	137
Total days on study (days)	14932	12977
Flare rate	0.00817	0.01056
Risk ratio (vs vehicle)	0.774	-
P-value (permutation test)	0.187	
Secondary efficacy result(s)– Full analysis set		
Ranked Flare	Pimecrolimus 1%	Vehicle
Total		
None	39 (45.9)	33 (37.9)
1	16 (18.8)	20 (23.0)
2	14 (16.5)	11 (12.6)
3 or more	16 (18.8)	23 (26.4)
Completed		
None	36 (42.4)	19 (21.8)
1	15 (17.6)	18 (20.7)
2	14 (16.5)	8 (9.2)
3 or more	15 (17.6)	21 (24.1)
Discontinued		
None	3 (3.5)	14 (16.1)
1	1 (1.2)	2 (2.3)
2	0	3 (3.4)
3 or more	1 (1.2)	2 (2.3)
P-value (Cochran-Mantel-Haenszel test)	0.001	
Time to First Flare	Pimecrolimus 1%	Vehicle
Lower quartile	42.0	8.0
Median	154.0	42.0
Estimated flare rate (95% confidence interval)	0.555 (0.448 - 0.662)	0.710 (0.604 - 0.815)
P-value (Log-rank test)	0.009	
Post-hoc analysis for Efficacy – Full analysis set		
Number of Flare (Adjusted)	Pimecrolimus 1%	Vehicle
Total number of flares (times)	126	177
Total days on study (days)	15037	14471
Flare rate	0.00838	0.01223
Risk ratio (vs vehicle)	0.685	-
P-value (permutation test)	0.035	
Safety Results		
Patients with Adverse Events and Adverse Events by System Organ Class		
Patients studied	Pimecrolimus 1%	Vehicle

Total no. of patients	85	87
Total no. with adverse events	58 (68.2)	55 (63.2)
10 Most Frequently Reported AEs Overall by Preferred Term		
	Pimecrolimus 1%	Vehicle
Nasopharyngitis	19 (22.4)	18 (20.7)
Eosinophil count increased	16 (18.8)	7 (8.0)
Folliculitis	11 (12.9)	7 (8.0)
Application site irritation	10 (11.8)	3 (3.4)
Blood lactate dehydrogenase increased	9 (10.6)	4 (4.6)
Acne NOS	6 (7.1)	4 (4.6)
Headache	4 (4.7)	4 (4.6)
Diarrhoea NOS	4 (4.7)	2 (2.3)
Dermatitis contact	4 (4.7)	0
Nausea	4 (4.7)	0
Serious Adverse Events and Deaths		
Patients studied	Pimecrolimus 1%	Vehicle
Total no. of patients	85	87
Death	0	0
Serious adverse events	1 (1.2)	2 (2.3)
AEs causing discontinuation	1 (1.2)	3 (3.4)
AEs causing temporary dose interruption	14 (16.5)	4 (4.6)
Other Relevant Findings–		

Date of Clinical Trial Report–	Under preparation	
Date Inclusion on Registry–	Nov 2005	
Date of Latest Update–	Nov 2005	