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 – CASM981C1301	
Title – Confirmatory study in pediatric patients with atopic dermatitis	
Phase of Development – III	
Study Start/End dates – 14-Nov-2003 through 24-Dec-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 pediatric patients with atopic dermatitis	
Centres – 31 centers in Japan	
Publication – on-going	

Objectives –

Primary outcome/efficacy objective(s) –

To evaluate topical application of pimecrolimus cream 1% and 0.6% 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 1% and 0.6% compared to vehicle in preventing flares using 'Ranked Flare' and 'Time to first flare'.

Test Product, Dose, and Mode of Administration –

Pimecrolimus cream 1%, 0.6% or vehicle was applied to affected area twice a day. When eczema worsened to severe or very severe, topical corticosteroids listed below were applied to affected area twice a day. After the remission of eczema by the treatment of topical corticosteroids, pimecrolimus cream 1%, 0.6% or vehicle was applied again.

Allowed topical corticosteroids for severe or very severe eczema
- Hydrocortisone butyrate on body/limbs
- Clobetasone butyrate on face/neck
- Prednisolone valerate acetate lotion on scalp

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. In emergent case, the indication for use topical corticosteroids via telephone was allowed.
- Patient applied topical corticosteroids within 3 days after the evaluation above.
- More than 7 days had passed since the patient had applied topical corticosteroids ointment during the last 'Flare'.

To evaluate the number of flares, 'Adjusted flare rate' was defined as the primary efficacy variable. Before calculating Adjusted flare rate, four flares were added and study duration were adjusted to 183 days in all patients that discontinued due to lack of efficacy. 'Adjusted 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

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

Secondary efficacy

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

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 2 to <16 years with AD according to the diagnostic criteria of Williams 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%	Pimecrolimus 0.6%	Vehicle
Planned N	80	80	80
Randomised n	83	79	78
Completed n (%)	70 (84.3)	74 (93.7)	63 (80.8)
Withdrawn n (%)	13 (15.7)	5 (6.3)	15 (19.2)
Included in the primary analysis n (%)	83 (100)	79 (100)	78 (100)
Withdrawn due to adverse events n (%)	5 (6.0)	0	3 (3.8)
Withdrawn due to lack of efficacy n (%)	5 (6.0)	3 (3.8)	6 (7.7)
Withdrawn for other reasons n (%)	3 (3.6)	2 (2.5)	6 (7.7)
Demographic and Background Characteristics			
N (ITT)	83	79	78
Females:males	36 : 47	42 : 37	42 : 36
Mean age, years (SD)	8.0 (3.6)	7.9 (3.1)	8.6 (3.5)
Mean height, cm (SD)	126.9 (21.9)	126.4 (19.5)	131.1 (20.8)
Mean weight, kg (SD)	30.4 (15.1)	29.1 (12.9)	32.4 (14.6)
Race			
White n (%)	0	0	0
Black n (%)	0	0	0
Asian n (%)	83 (100)	79 (100)	78 (100)
Other n (%)	0	0	0

Baseline IGA score (Baseline severity)			
2 (Mild)	24 (28.9)	28 (35.4)	26 (33.3)
3 (Moderate)	53 (63.9)	43 (54.4)	45 (57.7)
4 (Severe)	6 (7.2)	8 (10.1)	7 (9.0)
Primary Efficacy Result(s)– Full analysis set			
Adjusted Flare Rate	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Total number of flares (times)	91	98	155
Total days on study (days)	14164	14216	13131
Flare rate	0.00642	0.00689	0.01180
Risk ratio (vs vehicle)	0.544	0.584	-
P-value (permutation test)	0.003	0.008	
Primary Efficacy Result(s)– Per Protocol set			
Adjusted Flare Rate	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Total number of flares (times)	53	66	83
Total days on study (days)	10684	9445	8665
Flare rate	0.00561	0.00732	0.01091
Risk ratio (vs vehicle)	0.514	0.671	-
P-value (permutation test)	0.007	0.089	
Secondary efficacy result(s)– Full analysis set			
Ranked Flare	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Total			
None	48 (57.8)	41 (51.9)	28 (35.9)
1	14 (16.9)	13 (16.5)	18 (23.1)
2	10 (12.0)	8 (10.1)	13 (16.7)
3 or more	11 (13.3)	17 (21.5)	19 (24.4)
Completed			
None	38 (45.8)	40 (50.6)	23 (29.5)
1	13 (15.7)	11 (13.9)	13 (16.7)
2	8 (9.6)	6 (7.6)	12 (15.4)
3 or more	11 (13.3)	17 (21.5)	15 (19.2)
Discontinued			
None	10 (12.0)	1 (1.3)	5 (6.4)
1	1 (1.2)	2 (2.5)	5 (6.4)
2	2 (2.4)	2 (2.5)	1 (1.3)
3 or more	0	0	4 (5.1)
P-value (Cochran-Mantel-Haenszel test)	0.024	0.003	
Time to First Flare	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Lower quartile	51.0	56.0	10.0
Median	-	-	70.0
Estimated flare rate	0.448	0.487	0.672
(95% confidence interval)	(0.337 - 0.559)	(0.376 – 0.598)	(0.564 - 0.780)
P-value (Log-rank test)	0.002	0.007	
Safety Results			
Patients with Adverse Events and Adverse Events by System Organ Class			
Patients studied	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle

Total no. of patients	83	79	78
Total no. with adverse events	57 (68.7)	57 (72.2)	52 (66.7)
10 Most Frequently Reported AEs Overall by Preferred Term			
	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Nasopharyngitis	20 (24.1)	16 (20.3)	19 (24.4)
Eosinophil count increased	8 (9.6)	12 (15.2)	10 (12.8)
Folliculitis	8 (9.6)	7 (8.9)	8 (10.3)
Impetigo NOS	7 (8.4)	5 (6.3)	4 (5.1)
Application site irritation	5 (6.0)	3 (3.8)	1 (1.3)
Skin papilloma	5 (6.0)	3 (3.8)	1 (1.3)
Molluscum contagiosum	5 (6.0)	2 (2.5)	2 (2.6)
Upper respiratory tract inflammation	5 (6.0)	2 (2.5)	2 (2.6)
Blood lactate dehydrogenase increased	5 (6.0)	2 (2.5)	0
Blood bilirubin increased	1 (1.2)	5 (6.3)	0
Serious Adverse Events and Deaths			
Patients studied	Pimecrolimus 1%	Pimecrolimus 0.6%	Vehicle
Total no. of patients	83	79	78
Death	0	0	0
Serious adverse events	3 (3.6)	1 (1.3)	4 (5.1)
AEs causing discontinuation	2 (2.4)	1 (1.3)	2 (2.6)
AEs causing temporary dose interruption	10 (12.0)	14 (17.7)	8 (10.3)
Other Relevant Findings–			
Date of Clinical Trial Report–	Under preparation		
Date Inclusion on Registry–	Nov 2005		
Date of Latest Update–	Nov 2005		