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– Mild to moderate Atopic Dermatitis	
Study Number– CASM981CDE10	
Title– A 24-week, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study on pimecrolimus cream 1% assessing the steroid-sparing effect in the long term management of pediatric patients with severe atopic dermatitis	
Phase of Development– III	
Study Start/End dates– October 2003 / September 2004	
Study Design/Methodology–Multicenter, double-blind, randomized, vehicle-controlled, parallel-group study in patients 2- <18 years of age	
Centres– 22 centers in Germany	
Publication– on-going	
Objectives– *Primary outcome/efficacy objective(s)–* • To investigate the corticoid sparing effect of a 24-week treatment with pimecrolimus cream 1% in the long term management of severe pediatric AD. *Secondary outcome/efficacy objective(s)–* • To investigate if there is superior disease control when pimecrolimus cream 1% is given in addition to standard therapy in the long term management of severe pediatric AD. • To evaluate the safety of a 24-week treatment with pimecrolimus cream 1% in patients aged 2- <18 years suffering from severe AD. • To assess the quality of life in pediatric patients with severe AD and in their parents. d) To investigate the pharmaco-economic impact of the treatment with pimecrolimus cream 1% in this patient group.	
Test Product, Dose, and Mode of Administration–.pimecrolimus cream twice daily on the respective test area	
Reference Product(s), Dose(s), and Mode(s) of Administration – Vehicle cream once daily on the respective test area.	
Criteria for Evaluation– *Primary efficacy:* Percentage of days on which the patient decides to use corticosteroids instead of study medication. *Secondary efficacy:* Amount of corticosteroids required (averaged over study duration [mg/day]), the number of flares from baseline to week 24, the IGA, Eczema Area Severity Index (EASI), a daily Patient's Overall Self-Assessment score and a severity score of pruritus and sleep loss. *Safety/tolerability:*. Type, frequency and severity of AEs, safety lab.	
Statistical Methods– In the protocol it was planned to use a Wilcoxon test for the analysis of the primary endpoint, since its distribution was expected to be highly skewed. During a blind data review it was seen that although the raw data were heavily tailed, the distribution of the (studentized) residuals from the linear model variable = center, age class, baseline affected body area and baseline EASI looked reasonably normal to justify a parametric analysis. Since especially baseline EASI seemed to be highly prognostic,	

switching to an adjusted parametric analysis promised a higher precision for the estimation of treatment contrasts. Therefore, it was decided to use a parametric ANCOVA model with factors/covariates center, age class, baseline affected body area and baseline EASI for the analysis of the primary endpoint '% of days with Dermatop' as well as for the secondary endpoints 'amount of steroids' and 'mean post baseline EASI score'. The decision to modify the preplanned analysis was laid down in the RAMP Documentation (Module 3) prior to unblinding. After unblinding, an additional post-hoc analysis was performed for the subgroup of patients with high IGA Scores at screening (4 or 5)

Study Population: Inclusion/Exclusion Criteria and Demographics–.

Outpatients aged 2 to < 18 years with severe AD (score 8 or 9 according to Rajka and Langeland at the screening visit who responded to 21 days of treatment with prednicarbate cream 0.25% during the screening phase. Patients who had received phototherapy, systemic or topical therapy or systemic corticosteroids prior to study entry which could have an effect on AD were excluded from the study.

Number of Subjects	Pimecrolimus	Vehicle
Planned N	90	90
Randomised n	95	89
Completed n (%)	84 (88.4)	71 (79.8)
Withdrawn n (%)	11 (11.6)	18 (20.2)
Included in the primary analysis n (%)	95 (100)	89 (100)
Withdrawn due to adverse events n (%)	0	0
Withdrawn due to lack of efficacy n (%)	6 (6.3)	13 (14.6)
Withdrawn for other reasons n (%)	5 (5.3)	5 (5.6)
Demographic and Background Characteristics		
N (ITT)	95	89
Females:males	52 (54.7):43 (45.3)	43 (48.3):46 (51.7)
Mean age, years (SD)	5.1	4.7
Mean weight, kg (SD)	nd	nd
Race		
White n (%)	91 (95.8)	80 (89.9)
Black n (%)	1 (1.1)	1 (1.1)
Asian n (%)	3 (3.2)	6 (6.7)
Other n (%)	0 (0.0)	2 (2.2)

Primary Efficacy Result(s)–intent to treat population

Parameter	**Treatment Diff. (LS-Mean)**	**95% CL**	**p-Value**
Percentage of days with prednicarbate use (primary endpoint)	-4.8	[-11.8 , 2.3]	0.1841
Amount of prednicarbate applied per day [g/day]	0.0	[-0.2 , 0.2]	0.7798
EASI Score (mean over postbaseline assessments) [Pts]	-1.2	[-2.6 , 0.2]	0.0827
Mean flare duration [days]	3.2	[-5.3 , 11.7]	0.4597
Pct. of days with Dermatop (head neck)	-8.9	[-14.1 , -3.7]	0.0009
Pct. of days with Dermatop (rest of body)	-1.6	[-8.4 , 5.2]	0.6435

Negative numbers for the treatment difference indicate lower values for Elidel compared to Vehicle. Results from ANCOVA model: Variable = Center, Age class, Baseline affected body area, Baseline EASI score, Treatment

Secondary efficacy result(s)–ITT-population with IGA at screening = 4 or 5

Parameter	Treatment Diff. (LS-Mean)	95% CL	p-Value
Percentage of days with Dermatop use (primary endpoint)	-15.2	[-24.8 , -5.6]	0.0024
Amount of Dermatop applied per day [g/day]	-0.1	[-0.5 , 0.3]	0.5656
EASI Score (mean over postbaseline assessments) [Pts]	-2.9	[-4.9 , -1.0]	0.0041
Mean flare duration [days]	0.5	[-13.0 , 14.0]	0.9440
Pct. of days with Dermatop (head neck)	-20.3	[-29.5 , -11.1]	<.0001
Pct. of days with Dermatop (rest of body)	-9.7	[-19.2 , -0.2]	0.0462

Negative numbers for the treatment difference indicate lower values for Elidel compared to Vehicle. Results from ANCOVA model: Variable = Center, Age class, Baseline affected body area, Baseline EASI score, Treatment

Safety Results

Patients with Adverse Events and Adverse Events by System Organ Class

10 Most Frequently Reported AEs Overall by Preferred Term	Pimecrolimus	Vehicle
Nasopharyngitis	37 (38.9)	29 (32.6)
Cough	10 (10.5)	11 (12.4)
Rhinitis	11 (11.6)	8 (9.0)
Pyrexia	12 (12.6)	6 (6.7)
Headache	7 (7.4)	10 (11.2)
Bronchitis	7 (7.4)	8 (9.0)
Viral upper respiratory tract infection	8 (8.4)	7 (7.9)
Otitis media	7 (7.4)	7 (7.9)
Upper respiratory tract infection	7 (7.4)	6 (6.7)
Diarrhoea	5 (5.3)	6 (6.7)

Serious Adverse Events and Deaths

	TOTAL (N=184) n (%)	Elidel (N=95) n (%)	Vehicle (N=89) n (%)
All AEs	158 (85.9)	82 (86.3)	76 (85.4)
with suspected drug relation	9 (4.9)	5 (5.3)	4 (4.5)
leading to dose adjustment or temp. interruption	9 (4.9)	5 (5.3)	4 (4.5)
leading to permanent discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
requiring concomitant medication/non-drug therapy	141 (76.6)	70 (73.7)	71 (79.8)
Serious AEs	9 (4.9)	4 (4.2)	5 (5.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

SAEs with suspected drug relation	2 (1.1)	0 (0.0)	2 (2.2)
SAEs leading to permanent discontinuation	0 (0.0)	0 (0.0)	0 (0.0)

Other Relevant Findings– None

Date of Clinical Trial Report–	August 10, 2005 (draft)	
Date Inclusion on Registry–	September 30 2005	
Date of Latest Update–	September 16, 2005	