Sponsor–Novartis	**Web Page/Link to Prescribing/Label Information**– http://www.pharma.us.novartis.com/product/pi.jsp
Generic Drug Name– Pimecrolimus cream 1%	
Therapeutic Area of Trial– Dermatology	
Approved Indication– Mild/moderate atopic dermatitis, >2 yr age	
Study Number–ASM981 C2402	
Title– An exploratory, randomized, double-blind, vehicle-controlled, multicenter, parallel dose study investigating the use of pimecrolimus cream 1% in mild to moderate atopic dermatitis patients who demonstrate a clinical insensitivity to topical glucocorticoids	
Phase of Development–IV	
Study Start/End dates– 25-Sep-2002 / 17-Nov-2003	
Study Design/Methodology– An exploratory, randomized, double-blind, placebo-controlled, multicenter, parallel group study in pediatric and adult patients who have mild to moderate atopic dermatitis, and who have demonstrated a clinical insensitivity to topical glucocorticosteroid (a history of glucocorticoid insensitivity, AD colonized with S. aureus, and an Eczema Area and Severity Index (EASI) that did not decrease by >35% during treatment with prednicarbate emollient cream during 2 week screen period).	
Centres– United States (7), Canada (5), Switzerland (1).	
Publication–On-going	

Objectives–

Primary outcome/efficacy objective(s)–

- To explore the relationships between *S. aureus* colonization, superantigen production, peripheral blood mononuclear cells (PBMC) sensitivity to glucocorticoids and clinical presentation in patients with mild to moderate atopic dermatitis who demonstrate a clinical insensitivity to topical glucocorticoids.

Secondary outcome/efficacy objective(s)–

- To investigate the effectiveness of pimecrolimus cream in patients with mild to moderate atopic dermatitis who demonstrate a clinical insensitivity to topical glucocorticoids; To explore the safety of pimecrolimus cream in patients with mild to moderate atopic dermatitis who demonstrate a clinical insensitivity to topical glucocorticoids; To investigate the prevalence and role of *S. aureus* derived superantigens (SAG); To assess the glucocorticoid sensitivity of PBMCs from patients with mild to moderate atopic dermatitis

Test Product, Dose, and Mode of Administration– Investigational drug: Pimecrolimus Cream 1% was supplied in 50g tubes and applied in a thin film BID PRN to affected areas.

Reference Product(s), Dose(s), and Mode(s) of Administration– Matching placebo (vehicle) cream was supplied in 50g tubes, and applied in a thin film BID PRN to affected areas.

Criteria for Evaluation–

Primary efficacy: The primary efficacy parameters combined laboratory and clinical parameters. The laboratory parameters were S. aureus colonization in the four most affected eczematous lesions, superantigens, and clinical insensitivity to steroids (measured by IC50). The clinical parameters (defined in more detail below) were EASI, whole body IGA score, pruritus assessment score, patient's assessment score of disease control, and TLS for these four most affected lesions (local IGA scores).

Secondary efficacy: Eczema Area Severity Index (EASI) assessed by the investigator as the proportional body surface areas of disease involvement ranging from 0=0% to 6=90-100%, and the severity of erythema, infiltration/papulation, excoriation, and lichenification, each ranging from 0=none to 3=severe

Investigator's Global Assessment (IGA) scores (an ordinal scale ranging from 0=clear to 5=very severe disease to evaluate the overall severity of disease at the time of the assessment).

Other signs and symptoms of AD - assessed by the investigatory as the absence (0) or presence (1) of secondary signs and symptoms of AD (oozing/crusting, hyperpigmentation, hypopigmentation, dry skin/xerosis, and other).

Severity score of pruritus - assessed by the patient or patient caregiver as the severity of itching during the 24 hours prior to the assessment using a 4-point scale ranging from 0=absent to 3=severe.

Patient assessment - the level of disease control in the 7 days prior to the assessment using a 4 point scale ranging from 0=complete disease control to 3=uncontrolled disease.

Samples of the target lesions were obtained on moistened swabs were obtained to determine *S. aureus* colonization. *S. aureus* were identified through colony morphology (Gram-positive, cluster-forming coccus), catalase activity (positive), and coagulase activity (positive). A rough quantitation of S. aureus colonization was determined. *S. aureus* colonies were isolated for the detection of staphylococcal enterotoxins, exfoliative toxins, and toxic shock toxin-1 genes.

Safety/tolerability: Assessed through recording of adverse event (AE) reports, including serious adverse events (SAEs), and local tolerability.

Other: N/A

Pharmacology: not applicable

Statistical Methods – The primary analysis was the analysis of linear relationship between each laboratory parameter and each clinical parameter with respect to the change from baseline to Week 6, and from screening to baseline, as appropriate. Linearity was assessed using Pearson and Spearman correlation coefficients and separately via linear regression models. For both analyses, all intent-to-treat patients were combined (i.e., pimecrolimus cream and placebo data were pooled) Bootstrapping methods were used to obtain confidence intervals for the correlation coefficients.

Study Population: Inclusion/Exclusion Criteria and Demographics – Included were patients of either gender and any race between the ages of 2 and 50 years with mild to moderate AD affecting at least 5% of body surface area, and with a demonstrated poor response to treatment with prednicarbate emollient cream.

Patients were excluded for any treatments or clinical conditions that could interfere with the study evaluations including: concurrent skin disease in the treatment area; systemic malignancy or active lymphoproliferation; hypersensitivity to the study drug, it's components, and/or prednicarbate emollient cream; phototherapy, systemic or topical therapy (including systemic corticosteroids) known or suspected to have an effect on AD within four weeks prior to baseline; systemic retinoids or investigational drugs within eight weeks prior to baseline; systemic or topical antibiotics within two weeks prior to baseline.

Number of Subjects	Pimecrolimus cream 1%	Vehicle
Planned N	40	20
Randomised n	47	26
Completed n (%)	38 (80.9)	18 (69.2)
Withdrawn n (%)	9 (19.1)	8 (30.8)
Included in the primary analysis n (%)	46 (97.9)	26 (100)
Withdrawn due to adverse events n (%)	3 (6.4)	2 (7.7)
Withdrawn due to lack of efficacy n (%)	3 (6.4)	4 (15.4)
Withdrawn for other reasons n (%)	3 (6.4)	2 (7.7)
Demographic and Background Characteristics		
N (ITT)	46	26
Females:males	29:18	12:14
Mean age, years (SD)	18.3 (12.9)	18.8 (15.3)
Mean weight, kg (SD)	n.a.	n.a.

Race		
White n (%)	26 (55.3)	19 (73.1)
Black n (%)	12 (25.5)	4 (15.4)
Asian n (%)	2 (4.3)	2 (7.7)
Other n (%)	7 (14.9)	1 (3.8)

Primary Efficacy Result(s)–intent to treat population

Summary of primary efficacy correlations at Week 6 (ITT population)

Parameter	Sample size	Statistic	Correlation coefficient	95% confidence interval	p-value
IGA and *S. aureus*	66	Pearson	0.354	(0.18 , 0.51)	0.004**
		Spearman	0.358	(0.15 , 0.53)	0.003**
Pruritus severity and *S. aureus*	66	Pearson	0.287	(0.06 , 0.50)	0.020*
		Spearman	0.306	(0.08 , 0.51)	0.013*
Patient assessment and *S. aureus*	66	Pearson	0.302	(0.08 , 0.49)	0.014*
		Spearman	0.286	(0.05 , 0.49)	0.020*
EASI and *S. aureus*	66	Pearson	0.013	(-0.20 , 0.24)	0.919
		Spearman	0.052	(-0.20 , 0.30)	0.678

Pearson correlation based on data; Spearman correlations based on ranks of data; 95% confidence interval calculated using bootstrap methods with 5000 samples.
p-values: * p<0.05, ** p<0.01, *** p<0.001

Secondary efficacy result(s)–intent to treat population

Percent change in overall EASI by baseline score at Week 6 (ITT, LOCF)

	Statistic	Elidel	Placebo
EASI - % change from baseline	N	46	26
	Mean (SD)	1.8 (81.3)	26.9 (99.8)
	Median	-13.4	-7.9
Baseline overall EASI score			
Clear/Almost clear (Baseline EASI 0-<5)	N	15	9
	Mean (SD)	36.6 (117.3)	71.3 (144.1)
	Median	-2.3	-3.7
	Range	-83.3 - 260.4	-67.1 - 350.0
Mild/Moderate (Baseline EASI 5-<19)	N	18	9
	Mean (SD)	-19.7 (59.3)	10.7 (65.7)
	Median	-45.4	12.5
	Range	-86.8 - 145.9	-67.4 - 101.1
Severe/Very severe (Baseline EASI ≥19)	N	13	8
	Mean (SD)	-8.6 (37.6)	-4.9 (53.7)
	Median	-9.4	-25.9
	Range	-81.5 - 77.8	-53.1 - 94.6

Summary of additional efficacy variables at Week 6 (ITT, LOCF)

	Elidel N=46	Placebo N=26
Target lesion score - absolute change from baseline		
Mean TLS (SD)	-0.4 (1.1)	-0.5 (1.1)
Mean change in combined TLS (SD)	-0.4 (0.8)	-0.2 (0.7)
IGA - n (%) of patients		
Improvement	14 (30.4)	5 (19.2)
Treatment success (score = 0 or 1)	5 (10.9)	0 (0)
***S. aureus* counts - % change from baseline**		
Mean	-44.6	-89.6
Median	-90.0	-100.0
Pruritus - n (%) of patients		
Improvement	8 (17.4)	9 (34.6)
Absent or mild (score = 0 or 1)	12 (26.1)	6 (23.1)
Patient assessment - n (%) of patients		
Improvement	10 (21.7)	7 (26.9)
Complete or good disease control (score = 0 or 1)	14 (30.4)	6 (23.1)
Time to IGA improvement (Kaplan-Meier estimate)		
Median	>6 wk in either group	

Summary of highly significant (p<0.001) correlations between change and percent change from screening to baseline in EASI score, TLS score and *S. aureus* with the presence of each combination of superantigens (ITT population, n=72)

		Combination of superantigens presented by superantigen group			
	Correlation coefficient (p<0.001)	**I**	**II**	**III**	**V**
EASI change	-0.425	TST	SEG	SEA, SED, SEE, SEJ, SEN, SEO	SEI, SEK, SEM
EASI change	+ 0.507		SEC	SED, SEE, SHE, SEJ	SEK
EASI % change	+ 0.390			SEJ	SEK, SEM
S. aureus % change	+ 0.455		SEB, SEG	SEA, SED, SEE, SHE, SEJ, SEN, SEO	SEI, SEK, SEL, SEM, SEQ
S. aureus % change	+ 0.455		SEA	SED, SEE, SEH, SEJ	SEL
S. aureus % change	+ 0.409	TST	SEG	SED, SEE, SEJ, SEN, SEO	SEI, SEM
S. aureus % change	+ 0.455			SED, SEH	SEL

				SEJ	
TLS change	- 0.445	TST	SEB, SEG	SEA, SEE, SEJ, SEN, SEO	SEI SEK SEM
TLS % change	+ 0.616	TST		SEA, SEE, SEN	

SE (Staphylococcal enterotoxin); TST (Toxic Shock Syndrome Toxin)

Safety Results

Number (%) of patients with most frequent AEs (>= 4.0% in any treatment group) during the study, by primary system organ class, preferred term and treatment (Safety population and OL population)

	Double-blind						Open-label	
	Elidel N=47 n (%)		Placebo N=26 n (%)		Total N=73 n (%)		N=53 n (%)	
Total number of patients with an AE	28	(59.6)	13	(50.0)	41	(56.2)	29	(54.7)
Total number of AEs	89	n.a.	26	n.a.	115	n.a.	70	n.a.
Primary system organ class Preferred term								
Infections and infestations	**19**	**(40.4)**	**7**	**(26.9)**	**26**	**(35.6)**	**18**	**(34.0)**
Upper respiratory tract infection	5	(10.6)	2	(7.7)	7	(9.6)	9	(17.0)
Nasopharyngitis	4	(8.5)	1	(3.8)	5	(6.8)	1	(1.9)
Skin infection	3	(6.4)	1	(3.8)	4	(5.5)	3	(5.7)
Herpes simplex	2	(4.3)	0	(0.0)	2	(2.7)	2	(3.8)
General disorders and administration site conditions	**11**	**(23.4)**	**4**	**(15.4)**	**15**	**(20.5)**	**5**	**(9.4)**
Pyrexia	5	(10.6)	0	(0.0)	5	(6.8)	1	(1.9)
Application site pruritus	4	(8.5)	2	(7.7)	6	(8.2)	3	(5.7)
Application site burning	2	(4.3)	2	(7.7)	4	(5.5)	1	(1.9)
Application site pain	2	(4.3)	0	(0.0)	2	(2.7)	0	(0.0)
Nervous system disorders	**13**	**(27.7)**	**0**	**(0.0)**	**13**	**(17.8)**	**6**	**(11.3)**
Headache	11	(23.4)	0	(0.0)	11	(15.1)	6	(11.3)
Respiratory, thoracic and mediastinal disorders	**6**	**(12.8)**	**2**	**(7.7)**	**8**	**(11.0)**	**5**	**(9.4)**
Wheezing	2	(4.3)	1	(3.8)	3	(4.1)	2	(3.8)
Cough	2	(4.3)	1	(3.8)	3	(4.1)	0	(0.0)
Nasal congestion	2	(4.3)	0	(0.0)	2	(2.7)	0	(0.0)
Pharyngolaryngeal pain	2	(4.3)	0	(0.0)	2	(2.7)	0	(0.0)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within a primary system organ class is counted only once in that class.

Data are presented in descending frequency in the pimecrolimus double-blind treatment group.

10 Most Frequently Reported AEs Overall by Preferred Term	Pimecrolimus cream 1%	Vehicle
Headache	11 (23.4)	0

Upper respiratory tract infection	5 (10.6)	2 (7.7)
Pyrexia	5 (10.6)	0
Nasopharyngitis	4 (8.5)	1 (3.8)
Application site pruritus	4 (8.5)	2 (7.7)
Skin infection	3 (6.4)	1 (3.8)
Herpes simplex	2 (4.3)	0
Application site burning	2 (4.3)	2 (7.7)
Application site pain	2 (4.3)	0
Wheezing	2 (4.3)	1 (3.8)
Serious Adverse Events and Deaths		
Patients studied Serious events Deaths	47 0 0	26 0 0
Other Relevant Findings–		
Date of Clinical Trial Report–	02-Feb-2005	
Date Inclusion on Registry–	Feb 2005	
Date of Latest Update–	Oct 2005	