Sponsor– NOVARTIS

Generic Drug Name– pimecrolimus cream 1%

Therapeutic Area of Trial– Dermatology

Approved Indication– Mild/moderate atopic dermatitis, >2 yr age

Study Number– CASM981CUS04

Title– A 6-month, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of pimecrolimus cream 1% twice daily vs standard of care in the management of mild to severe atopic dermatitis in children 3 months to 11 years

Phase of Development– Phase 3b

Study Start/End dates– 05-Oct-2001 / 06-Nov-2002

Study Design/Methodology – This was a double-blind, multicenter, randomized, vehicle-controlled, parallel-group comparative study in children, using pimecrolimus cream 1% BID versus standard-of-care therapy.

Centres– 35 sites in the United States

Publication–

Objectives–

Primary outcome/efficacy objective(s)–

- The primary objective of this study was to compare the efficacy and safety of ASM 981 (pimecrolimus) cream 1% foundation therapy and standard-of-care therapy over a 6-month treatment period in children (3 months to 11 years) with mild to severe atopic dermatitis (AD).

Secondary outcome/efficacy objective(s)–

The secondary objectives of this study were to:

- Compare the total corticosteroid exposure of children treated with pimecrolimus foundation therapy with that of those receiving standard-of-care therapy;
- Evaluate the major signs/symptoms of children with mild to severe AD treated with pimecrolimus versus standard-of-care therapy;
- Explore the synergistic potential of pimecrolimus cream 1% and topical corticosteroids used during the same time frame to treat atopic dermatitis disease flares;
- Assess the quality of life of pediatric AD patients and their caregivers in each treatment group.

Test Product, Dose, and Mode of Administration–. Topical pimecrolimus cream 1%

Reference Product(s), Dose(s), and Mode(s) of Administration – Topical vehicle cream

Criteria for Evaluation–

Primary efficacy: The primary efficacy variable was the percentage of patients with no flares over the 24-week treatment period.

Secondary efficacy:

- Percentage of patients with 0 or 1 flare over the 24-week treatment period
- Number of days of corticosteroid use
- Number of flares over the 24-week treatment period
- Average (per patient) flare duration in days
- Average (per patient) number of days between flares
- Percentage of patients discontinued due to unsatisfactory therapeutic effect
- Global rating of change

Safety/tolerability: Safety variables for the study were reported adverse events (AEs); reported serious adverse events (SAEs); physical examinations; vital signs (blood pressure and pulse rate); and laboratory evaluations. A serum pregnancy test was performed for all female patients of childbearing potential at the screening visit and at the end or early discontinuation of the study.

Other: N/A

Pharmacology: There were no pharmacokinetic assessments for this study.

Statistical Methods– Safety was assessed primarily through the recording of AEs and observation of the number of laboratory values that fell outside of predetermined ranges. Vital signs, and other special tests were recorded as well. Statistical analyses of crude incidences (utilizing Fisher exact test), incidence density rates (using Poisson regression), time to first occurrence (using Kaplan-Meier), for the entire safety population, as well as 2 subgroup populations (patients aged <24 months and patients >24 months) were conducted on AEs.

The primary efficacy variable was summarized by frequency and percentage and was analyzed using the Cochran-Mantel-Haenszel test, adjusting for center. The number of flares over the 24-week treatment period was analyzed using a Poisson regression model with treatment and center as factors. Number of days of corticosteroid use, average (per patient) flare duration in days, and average (per patient) number of days between flares were each analyzed using an analysis of variance (ANOVA) model that included treatment and center as main effects. Percentage of patients with 0 or 1 flare over the 24-week treatment period, percentage of patients discontinued due to unsatisfactory therapeutic effect, percentage of patients with pruritus severity assessment score of 0 or 1, percentage of patients with Investigator's Global Assessment score of 0 or 1, and percentage of patients with Patient's Self Assessment by caregiver score of 0 or 1 were analyzed using a Cochran-Mantel-Haenszel test, adjusting for center. Global rating of change (5-point scale) was analyzed using a van Elteren test, adjusting for center. No interim analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics– The target population for this study was male or female patients aged 3 months to 11 years with mild to severe AD, as determined by an Investigator's Global Assessment (IGA) score of 2 (mild), 3 (moderate) or 4 (severe), and having atopic dermatitis affecting = 5% total body surface area based on rule of 9s, on a stable dose of an allowed bland emollient for at least 1 week at baseline, and who were outpatients at baseline (Day 1). Diagnosis of atopic dermatitis was confirmed using diagnostic criteria of Sampson (1990) in patients younger than 2 years of age and diagnostic criteria of Williams et al (1994) in patients 2 years of age and older. The legal guardian was to have been informed of the study procedures and have signed the informed consent approved for the study. Female patients of childbearing potential were excluded if they were pregnant, breastfeeding, or not practicing a medically approved method of contraception during and up to at least 4 weeks after the end of treatment. Patients were also excluded for use of any systemic therapy within 1 month of study start, any topical therapy other than a low-potency to mid-potency topical corticosteroid within 7 days of study start, being immunocompromised, or having any active infection or concurrent skin condition that would interfere with evaluation.

Number of Subjects

Disposition	ASM N=183 n (%)	Vehicle N=92 n (%)	Total N=275 n (%)
Total no. of patients -			
Randomized	183	92	275
Completed[1]	150 (82.0)	66 (71.7)	216 (78.5)
ITT Population[1]	181 (98.9)	91 (98.9)	272 (98.9)
Safety Population[1]	183 (100.0)	92 (100.0)	275 (100.0)
Infant subgroup[2]	41 (22.6)	21 22.8)	62 (22.5)
Older children subgroup[3]	142 (77.6)	71 (77.2)	213 (77.5)
Discontinuations			
Lost to follow-up	14 (7.7)	6 (6.5)	20 (7.3)
Unsatisfactory therapeutic effect	7 (3.8)	13 (14.1)	20 (7.3)
Patient withdrew consent	8 (4.4)	4 (4.3)	12 (4.4)
Adverse events	4 (2.2)	3 (3.3)	7 (2.5)

Notes: Randomized=all enrolled patients who were randomized to receive trial medication.
ITT population=all randomized patients who took at least one dose of trial medication ad from whom at least 1 post baseline measurement was obtained.
Safety population=all randomized patients who took at least 1 dose of randomized medication.
[1]Percentage uses number randomized as the denominator.
[2]Patients aged 3 months to 23 months
[3]Patients aged 24 months to 11 years

Demographic and Background Characteristics

Characteristic	ASM N=183 n (%)	Vehicle N=92 n (%)	Total N=275 n (%)
Sex			
Male	99 (54.1)	51 (55.4)	150 (54.5)
Female	84 (45.9)	41 (44.6)	125 (45.5)
P value[1]			0.657
Race			
Caucasian	93 (50.8)	36 (39.1)	129 (46.9)
Black	42 (23.0)	29 (31.5)	71 (25.8)
Oriental	9 (4.9)	5 (5.4)	14 (5.1)
Other	39 (21.3)	22 (23.9)	61 (22.2)
P value[1]			0.199
Age (months)			
Mean (SD)	59.0 (38.06)	61.8 (40.90)	59.9 (38.98)
Median	53	59	54
Min, Max	3, 140	3, 143	3, 143
P value[2]			0.477

Note: Statistical tests do not include patients in the missing category.
[1]P value is based on a Cochran-Mantel-Haenszel test, adjusting for center.
[2]P value is based on an ANOVA with treatment and center as main effects. One pooled center consisting of 6 low-enrolling Sites (2, 9, 14, 15, 20, 23) was used for analysis in addition to the remaining individual sites.

Primary Efficacy Result(s)–intent to treat population

Patients with:	ASM N=181 n (%)	Vehicle N=91 n (%)	Total N=272 n (%)	P value[1]
No flares over the 24-week treatment period[2]	94 (51.9)	31 (34.1)	125 (46.0)	0.007

Notes: A flare is determined by the investigator dispensing a flare regimen corticosteroid.
Nineteen patients had corticosteroid dispensed without an IGA score greater or equal to 4, meaning it may not have been actual flare occurrence. These patients are analyzed in this table due to the flare regimen corticosteroid dispensed to them. The total number of occurrences for these patients was 24.
[1]P value is based on a Cochran-Mantel-Haenszel test, adjusting for center.
[2]Any patient who drops out of the study without having experienced a flare will be treated as a nonresponder in the analysis.

Secondary efficacy result(s)–intent to treat population

Patients with	ASM N=181 n (%)	Vehicle N=91 n (%)	Total N=272 n (%)	P value[1]
0 or 1 flare over the 24-week treatment period[2]	120 (66.3)	44 (48.4)	164 (60.3)	0.006

Notes: A flare is determined by the investigator dispensing a flare regimen corticosteroid.
Nineteen patients had corticosteroid dispensed without an IGA score greater than or equal to 4, meaning it may not have been actual flare occurrence. These patients are analyzed in this table due to the flare regimen corticosteroid dispensed to them. The total number of occurrences for these patients is 24.
[1]P value is based on a Cochran-Mantel-Haenszel test, adjusting for center.
[2]Any patient who drops out of the study without having experienced a flare will be treated as a nonresponder in the analysis.

	Pimecrolimus	Vehicle	P- value
Mean Days of CS	10.9 days	17.3 days	P=0.02
Mean flares over 6 month period	0.7	1.3	P<0.001
Median per patient flare duration	14.5 days	13.3 days	P=0.096
Mean flare-free interval	42 days	27 days	

Patient with	ASM N=181 n (%)	Vehicle N=91 n (%)	Total N=272 n (%)	P value[1]
Discontinuation due to unsatisfactory therapeutic effect over the 24-week treatment period	7 (3.9)	13 (14.3)	20 (7.4)	0.003

[1]P value is based on a Cochran-Mantel-Haenszel test, adjusting for center

Global Rating of Change[1]	ASM N=181	Vehicle N=91	Total N=272	P value[2]
A lot better	69 (38.1)	23 (25.3)	92 (33.8)	0.143
Somewhat better	33 (18.2)	21 (23.1)	54 (19.9)	
About the same	44 (24.3)	26 (28.6)	70 (25.7)	
Somewhat worse	7 (3.9)	7 (7.7)	14 (5.1)	
A lot worse	2 (1.1)	0 (0.0)	2 (0.7)	
Missing	26 (14.4)	14 (15.4)	40 (14.7)	

Note: Statistical tests do not include patients in the missing category.
[1]Question reads: Considering the topics covered in the previous 28 questions, please use the scale below to indicate any changes in your quality of life since the start of the study. The assessment was made at the last study visit.
[2]P value is based on a van Elteren test, adjusting for center.

Safety Results

Patients with Adverse Events and Adverse Events by System Organ Class

System organ class	Crude incidence (%)			Incidence density per 1000 person-months follow-up		Kaplan-Meier incidence estimate at Day 169 (%)		
Preferred term	ASM (N=183)	Vehicle (N=92)	P value[1]	Relative Risk	Confidence interval	ASM (N=183)	Vehicle (N=92)	P value[2]
Eye disorders								
Conjunctivitis	2.2	3.3	0.69	0.629	0.334, 1.187	2.4	4.0	0.561
Gastrointestinal disorders								
Diarrhea NOS	6.0	2.2	0.231	2.596	1.167, 5.776	6.1	2.4	0.179
Vomiting NOS	6.6	7.6	0.803	0.809	0.455, 1.440	7.4	8.4	0.680
General disorders and administration site conditions								
Pyrexia	14.8	13.0	0.855	1.062	0.646, 1.746	15.1	14.8	0.802
Immune system disorders								
Seasonal allergy	2.7	3.3	>0.999	0.787	0.416, 1.487	3.1	4.1	0.757
Infections and infestations								
Ear infection NOS	4.4	7.6	0.272	0.539	0.309, 0.943	4.3	8.6	0.233
Gastroenteritis viral NOS	3.3	2.2	0.722	1.416	0.678, 2.958	1.2	1.1	0.989
Impetigo NOS	4.4	5.4	0.766	0.755	0.415, 1.374	4.9	7.1	0.635
Otitis media NOS	9.3	3.3	0.086	2.675	1.293, 5.530	9.8	3.7	0.088
Sinusitis	4.9	4.3	>0.999	1.062	0.562, 2.007	5.5	5.3	0.868
URI NOS	18.0	17.4	>0.999	0.973	0.608, 1.559	20.0	21.8	0.941
Injury, poisoning and procedural complications								
Arthropod bite	4.9	1.1	0.172	4.248	1.595, 11.316	5.7	1.4	0.157
Nervous system disorders								
Headache NOS	4.4	3.3	0.756	1.259	0.897, 3.975	4.7	4.0	0.666
Respiratory, thoracic, and mediastinal disorders								
Cough	13.1	14.1	0.852	0.871	0.535, 1.419	14.1	15.9	0.636
Nasal congestion	4.9	7.6	0.416	0.607	0.347, 1.060	5.4	8.4	0.344
Nasopharyngitis	8.7	12.0	0.398	0.687	0.404, 1.166	10.0	13.5	0.386
Pharyngitis	4.4	2.2	0.504	1.888	0.879, 0.053	4.7	2.6	0.367
Pharyngitis NOS	3.3	1.1	0.430	2.832	1.165, 6.886	4.1	1.5	0.300
Rhinitis allergic NOS	2.7	3.3	>0.999	0.787	0.417, 1.484	3.1	3.8	0.765

Rhinorrhea	9.8	2.2	0.025	4.248	1.765, 10.222	10.7	2.5	0.024
Wheezing	3.3	4.3	0.736	0.708	0.386, 1.299	3.8	4.9	0.589
Skin and subcutaneous tissue disorders								
Rash NOS	2.2	4.3	0.448	0.472	0.247, 0.902	2.4	4.4	0.309
Urticaria NOS	3.3	0	0.183	----	----, ----	3.6	0	0.087

Notes: If a patient experienced more than 1 episode of a particular adverse event, the patient was counted only once for that event. If a patient had more than 1 adverse event in a system organ class, the patient was counted only once for that system organ class.
[1]P value is based on Fisher exact test.
[2]P value is from a log-rank test based on the Kaplan-Meier method for the comparison of the 2 survival distributions (not for comparison of incidences on Day 169).
NOS = not otherwise specified, URI = upper respiratory tract infection

10 Most Frequently Reported AEs Overall by Preferred Term	**Crude Incidence (%) Pimecrolimus cream 1%**	**Crude Incidence (%) Vehicle**
URI, NOS	**18.0**	17.4
Pyrexia	**14.8**	13.0
Cough	13.1	**14.1**
Nasopharyngitis	8.7	**12.0**
Rhinorrhea	**9.8**	2.2
Otitis media NOS	**9.3**	3.3
Vomiting NOS	6.6	**7.6**
Nasal congestion	4.9	**7.6**
Ear infection NOS	4.4	**7.6**
Diarrhea NOS	**6.0**	2.2
Sinusitis NOS	**4.9**	4.3
Serious Adverse Events and Deaths		
	Pimecrolimus cream 1%	**Vehicle**
Deaths	**0**	**0**
Serious adverse events (SAEs)	**3**	**3**
AEs causing discontinuation	**4**	3
Other Relevant Findings–		
Date of Clinical Trial Report–	01-Dec-2004	
Date Inclusion on Registry–	14-Feb-2005	
Date of Latest Update–	Oct-2005	