| **Sponsor**– NOVARTIS | **Web Page/Link to Prescribing/Label Information**– 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–** CASM981CUS03 | |
| **Title–** A 6-month, randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of pimecrolimus 1% cream twice daily vs standard of care in the management of mild to severe atopic dermatitis in adults | |
| **Phase of Development–** Phase 3b | |
| **Study Start/End dates–** 05-Oct-2001 / 02-Feb-2003 | |
| **Study Design/Methodology–** This was a multicenter, randomized, parallel-group, double-blind, vehicle-controlled trial using pimecrolimus cream 1% twice daily versus standard of care therapy. | |
| **Centres–** 36 sites in the United States | |
| **Publication**– Ongoing | |

**Objectives–**

*Primary outcome/efficacy objective(s)–*

- To compare efficacy and safety of pimecrolimus cream 1% foundation therapy[1] to standard of care therapy[2] over a 6-month treatment period in adults with mild to severe atopic dermatitis.

*Secondary outcome/efficacy objective(s)–*

The secondary objectives of this study were to:

- Compare the total corticosteroid exposure of adults treated with ASM foundation therapy with that of those receiving standard of care therapy
- Evaluate the major signs/symptoms of adults with mild to severe atopic dermatitis treated with ASM versus standard of care therapy
- Explore the synergic potential of ASM and topical corticosteroids used during the same time frame to treat atopic dermatitis disease flares
- Assess the quality of life of patients with atopic dermatitis treated with ASM versus standard of care therapy

[1] Foundation therapy is emollients for underlying dry skin, pimecrolimus cream 1% at the earliest signs/symptoms of eczema, and topical corticosteroids for established flares.

[2] Conventional therapy is emollients for underlying dry skin and topical corticosteroids for established flares

**Test Product, Dose, and Mode of Administration–** pimecrolimus cream 1%, topical

**Reference Product(s), Dose(s), and Mode(s) of Administration–** Vehicle cream, topical

**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[3] over the 24-week treatment period
- Number of days of corticosteroid use

- Number of flares[3] over the 24-week treatment period
- Average per patient flare[3] duration in days
- Global rating of change
- Percentage of patients discontinued due to unsatisfactory therapeutic effect.

[3]A flare was determined by an investigator global assessment (IGA) score of 4 or 5.

*Safety/tolerability:*. Safety variables for the study comprised adverse events (AEs), serious adverse events (SAEs), physical examinations, vital signs (blood pressure and pulse rate), and laboratory evaluations.

*Other: NA*

*Pharmacology:* Not conducted

**Statistical Methods–** Data from 8 low-enrolling centers with 1, 2, or 3 patients were pooled for analysis of variance and analysis of covariance analyses. For the Poisson regression analysis, centers were pooled to accommodate low-enrolling sites, as well as centers with 0 flares only for both treatment groups. All statistical tests were conducted against a 2-sided alternative hypothesis, employing a significance level of 0.05.

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. Time (in days) to reach a pruritus severity assessment score of 0 or 1 and time (in days) to a pruritus severity assessment score improvement of at least 1 point were summarized using the product limit (Kaplan-Meier) method and the treatment groups were compared using a log-rank test and a Wilcoxon test. 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 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 a pruritus severity assessment score of 0 or 1, percentage of patients with an Investigator's Global Assessment score of 0 or 1, and percentage of patients with a Patient's Self-Assessment score of 0 or 1 were analyzed using a Cochran-Mantel-Haenszel test, adjusting for center. Change from baseline in the physical and mental component scores of SF-12 were each analyzed using an ANCOVA model that included treatment and center as main effects and baseline as a covariate, as well as a Wilcoxon rank sum test. Change from baseline in Eczema Area Severity Index (EASI), change from baseline in the total score of the Quality of Life of Atopic Dermatitis, and daily pruritus severity assessment score for Days 2 through 8 were each analyzed using an ANCOVA model that included treatment and center as main effects, and baseline as a covariate. Global rating of change (5-point scale) was analyzed using a van Elteren test, adjusting for center. No interim analyses were performed.

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), and time to first occurrence (using Kaplan-Meier method) were conducted on AEs (for the entire safety population).

**Study Population: Inclusion/Exclusion Criteria and Demographics–**. Male or female patients between 18 and 65 years of age with mild to severe atopic dermatitis, 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 (TBSA) based on rule of 9s, on a stable dose of an allowed bland emollient for at least 1 week at baseline, and who were out patients at baseline (Day 1). Diagnosis of atopic dermatitis was made using Hanafin and Rajka diagnostic criteria.

**Number of Subjects**

| Disposition | ASM N=176 n (%) | Vehicle N=88 n (%) | Total N=264 n (%) |
|---|---|---|---|
| Total no. of patients - | | | |
| Randomized | 176 | 88 | 264 |
| Completed[1] | 128 (72.7) | 65 (73.9) | 193 (73.1) |
| ITT Population[1] | 172 (97.7) | 86 (97.7) | 258 (97.7) |
| Safety Population[1] | 176 (100.0) | 88 (100.0) | 264 (100.0) |
| Discontinuations | | | |
| Lost to follow-up | 17 (9.7) | 6 (6.8) | 23 (8.7) |
| Unsatisfactory therapeutic effect | 9 (5.1) | 10 (11.4) | 19 (7.2) |
| Patient withdrew consent | 15 (8.5) | 5 (5.7) | 20 (7.6) |
| Adverse events | 6 (3.4) | 0 (0.0) | 6 (2.3) |
| Protocol violation | 1 (0.6) | 2 (2.3) | 3 (1.1) |

Source: Post-text tables 7.1-1 and 7.1-2

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 and 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.

**Demographic and Background Characteristics**

| Characteristic | ASM N=176 n (%) | Vehicle N=88 n (%) | Total N=264 n (%) |
|---|---|---|---|
| Sex | | | |
| Male | 54 (30.7) | 38 (43.2) | 92 (34.8) |
| Female | 122 (69.3) | 50 (56.8) | 172 (65.2) |
| P value[1] | | | 0.065 |
| Race | | | |
| Caucasian | 91 (51.7) | 55 (62.5) | 146 (55.3) |
| Black | 50 (28.4) | 19 (21.6) | 69 (26.1) |
| Oriental | 19 (10.8) | 7 (8.0) | 26 (9.8) |
| Other | 16 (9.1) | 7 (8.0) | 23 (8.7) |
| P value[1] | | | 0.314 |
| Age (years) | | | |
| Mean (SD) | 37.5 (11.51) | 39.3 (13.04) | 38.1 (12.04) |
| Median | 38 | 39 | 38 |
| Min, Max | 18, 69 | 18, 68 | 18, 69 |
| P value[2] | | | 0.387 |

Source: Post-text table 7.3-1

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 8 low-enrolling sites (12, 15, 20, 24, 25, 28, 29, 34) was used for analysis in addition to the remaining individual sites.

| Disease Characteristic | ASM N=176 | Vehicle N=88 | P value[5] |
|---|---|---|---|
| IGA (mean)[1] | 3.0 | 3.0 | 0.935 |
| EASI (mean)[2] | 12.0 | 11.6 | 0.870 |
| Pruritus Severity Score[3] (mean) | 2.0 | 2.0 | 0.749 |
| Total Body Surface Area Affected[4] (mean) | 23.49% | 21.48% | 0.386 |

Source: Post-text table 7.3-2

[1]IGA score: 0=Clear, 1=Almost Clear, 2=Mild disease, 3=Moderate disease, 4=Severe disease, 5=Very severe disease.

[2]EASI score is a composite score measuring severity and extent of atopic dermatitis.

[3]Pruritus severity score: 0=Absent, 1=Mild, 2=Moderate, 3=Severe.

[4]EASI-derived TBSA is calculated using body region area affected in head/neck, trunk, upper limbs and lower limbs.

[5]P value is based on an ANOVA with treatment and center as main effects. One pooled center consisting of 8 enrolling sites (12, 15, 20, 24, 25, 28, 29, 34) was used for analysis in addition to the remaining individual sites.

**Primary Efficacy Result(s)–intent to treat population**

| Patients with: | ASM N=172 n (%) | Vehicle N=86 n (%) | Total N=258 n (%) | P value[1] |
|---|---|---|---|---|
| No flares over the 24-week treatment period | 69 (40.1) | 28 (32.6) | 97 (37.6) | 0.206 |

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

[2]Any patient who dropped out of the study without having experienced a flare was treated as a nonresponder in the analysis.

**Secondary efficacy result(s)–intent to treat population**

| | Pimecrolimus | Control | p-value |
|---|---|---|---|
| **Mean Days of CS Use** | 13 days | 21.3 days | 0.005 |
| | | | |

Summary of number of flares over the 24-week treatment period by treatment (ITT population)

| Summary statistics (over 24-week treatment period) | ASM 981 cream 1% N = 172 | ASM 981 vehicle cream N = 86 | ASM 981 cream 1% versus vehicle cream p-value |
|---|---|---|---|
| n | 172 | 86 | 0.003 |
| Mean number of flares (SD) | 0.8 (1.19) | 1.2 (1.41) | |
| Median | 0 | 1 | |
| Min, Max | 0, 5 | 0, 5 | |
| Patients with | | | |
| 0 flares | 97 (56.4%) | 39 (45.3%) | |
| 1 flare | 34 (19.8%) | 15 (17.4%) | |
| 2 flares | 25 (14.5%) | 12 (14.0%) | |
| 3 flares | 8 (4.7%) | 14 (16.3%) | |
| 4 flares | 5 (2.9%) | 4 (4.7%) | |
| 5 flares | 3 (1.7%) | 2 (2.3%) | |

| Patients with | ASM N=172 n (%) | Vehicle N=86 n (%) | Total N=258 n (%) | P value[1] |
|---|---|---|---|---|
| 0 or 1 flare over the 24-week treatment period[2] | 93 (54.1) | 38 (44.2) | 131 (50.8) | 0.087 |

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

[2]Any patient who dropped out of the study without having experienced a flare was treated as a nonresponder in the analysis.

| Global Rating of Change[1] | ASM N=172 | Vehicle N=86 | Total N=258 | P value[2] |
|---|---|---|---|---|
| A lot better | 42 (24.4) | 21 (24.4) | 63 (24.4) | 0.526 |
| Somewhat better | 52 (30.2) | 20 (23.3) | 72 (27.9) | |
| About the same | 55 (32.0) | 31 (36.0) | 86 (33.3) | |
| Somewhat worse | 7 (4.1) | 6 (7.0) | 13 (5.0) | |
| A lot worse | 1 (0.6) | 0 (0.0) | 1 (0.4) | |
| Missing | 15 (8.7) | 8 (9.3) | 23 (8.9) | |

[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.

| Patients with | ASM N=172 n (%) | Vehicle N=86 n (%) | Total N=258 n (%) | P value[1] |
|---|---|---|---|---|
| Discontinuation due to unsatisfactory therapeutic effect over the 24-week treatment period | 9 (5.2) | 10 (11.6) | 19 (7.4) | 0.052 |

Source: Post-text table 9.1-1

[1]P value is based on a Cochran-Mantel-Haenszel 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=176) | Control (N=88) | P value[1] | Relative Risk | Confidence interval | ASM (N=176) | Control (N=88) | P value[2] |
| ***Gastrointestinal disorders*** | | | | | | | | |
| Abdominal pain upper | 0.6 | 2.3 | 0.258 | 0.239 | 0.113, 0.505 | 7.0 | 2.7 | 0.204 |
| Diarrhea NOS | 3.4 | 0 | 0.183 | ---- | ---- | 3.7 | 0 | 0.087 |
| ***General disorders and administration site conditions*** | | | | | | | | |
| Application site burning | 4.5 | 0 | 0.055 | ---- | ---- | 4.8 | 0 | 0.048 |
| ***Infections and infestations*** | | | | | | | | |
| Influenza | 4.0 | 1.1 | 0.276 | 3.343 | 1.308, 8.540 | 4.3 | 1.3 | 0.219 |
| Sinusitis NOS | 3.4 | 3.4 | >0.999 | 0.955 | 0.493, 1.851 | 4.0 | 4.5 | 0.973 |
| Skin bacterial infection | 4.5 | 1.1 | 0.279 | 3.820 | 1.405, 10.383 | 5.1 | 1.6 | 0.164 |
| URI NOS | 10.8 | 6.8 | 0.376 | 1.512 | 0.827, 2.763 | 12.9 | 8.1 | 0.360 |
| ***Injury, poisoning and procedural complications*** | | | | | | | | |
| Post procedural pain | 1.7 | 2.3 | >0.999 | 0.716 | 0.364, 1.410 | 1.9 | 3.1 | 0.716 |
| ***Musculoskeletal and connective tissue disorders*** | | | | | | | | |
| Back pain | 0.6 | 3.4 | 0.109 | 0.159 | 0.075, 0.339 | 7.0 | 5.8 | 0.065 |
| Myalgia | 0.6 | 2.3 | 0.258 | 0.239 | 0.114, 0.500 | 6.0 | 1.5 | 0.201 |
| ***Nervous system disorders*** | | | | | | | | |
| Headache | 7.4 | 2.3 | 0.155 | 3.104 | 1.354, 7.117 | 8.5 | 2.4 | 0.111 |
| ***Psychiatric disorders*** | | | | | | | | |
| Anxiety | 0.6 | 2.3 | 0.258 | 0.239 | 0.114, 0.500 | 7.0 | 3.2 | 0.194 |
| ***Respiratory, thoracic, and mediastinal disorders*** | | | | | | | | |
| Asthma aggravated | 1.1 | 2.3 | 0.603 | 0.478 | 0.234, 0.974 | 1.2 | 2.7 | 0.449 |
| Asthma NOS | 2.3 | 0 | 0.305 | ---- | ---- | 2.9 | 0 | 0.169 |
| Nasal congestion | 1.1 | 3.4 | 0.337 | 0.318 | 0.163, 0.620 | 1.2 | 3.8 | 0.185 |
| Nasopharyngitis | 7.4 | 13.6 | 0.120 | 0.517 | 0.308, 0.868 | 6.9 | 18.5 | 0.080 |
| Pharyngitis | 1.1 | 6.8 | 0.018 | 0.159 | 0.097, 0.378 | 1.6 | 8.5 | 0.009 |
| ***Skin and subcutaneous tissue disorders*** | | | | | | | | |
| Contusion | 0 | 2.3 | 0.110 | 0 | ---- | 0 | 2.4 | 0.041 |

[1]P value is based on Fisher exact test

[2]P value is from a log-rank test based on the Kaplan-Meier method

NOS = not otherwise specified, URI = upper respiratory tract infection

| **10 Most Frequently Reported AEs Overall by Preferred Term** | Pimecrolimus Crude incidence (%) | Control Crude incidence (%) |
|---|---|---|
| Nasopharyngitis | 7.4 | **13.6** |
| URI, NOS | **10.8** | 6.8 |
| Headache | **7.4** | 2.3 |
| Pharyngitis | 1.1 | **6.8** |
| Skin bacterial infection | **4.5** | 1.1 |
| Application site burning | **4.5** | 0 |
| Sinusitis NOS | **3.4** | **3.4** |
| Nasal congestion | 1.1 | **3.4** |
| Back pain | 0.6 | **3.4** |
| Diarrhea NOS | **3.4** | 0 |

**Serious Adverse Events and Deaths**

| | Pimecrolimus | Control |
|---|---|---|
| Deaths | 0 | 0 |
| Serious AEs | **4** | 2 |
| Discontinuations due to AEs | **6** | 0 |

| | | |
|---|---|---|
| **Other Relevant Findings–** | | |
| **Date of Clinical Trial Report–** | 04-Aug-2003 | |
| **Date Inclusion on Registry–** | 14-Feb-2005 | |
| **Date of Latest Update–** | | |