

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-302

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-302

Original

NDA #21-302

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Sponsor: Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Generic name: pimecrolimus cream 1%

Proposed trade name: Elidel Cream, 1%

Chemical name: (1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-2-
{(1R,3R,4S)-4-chloro-3-methoxycyclohexyl}-1-methylvinyl]-17-
ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-
11,28-dioxa-4-aza-tricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-
tetraone.

Molecular formula: C₄₃H₆₈ClNO₁₁

Molecular weight: 810.47

Pharmacologic Category: Immunosuppressant

Proposed Indication(s): Atopic Dermatitis

Dosage Form(s): Cream

Route (s) of Administration: Topical

NDA Drug Classification: 1S

Related Reviews: Statistical Review dated: 10/22/01
Biopharm Review dated: pending
Micro Review dated: 6/15/01
Pharm/Tox Review dated: 9/24/01

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

ASM 1% cream, pimecrolimus cream, is approvable from a clinical perspective, for short-term and intermittent long-term therapy in the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 2 years of age and older _____ in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies. Double-blind placebo controlled trials done in pediatric patients ages 3 months - 17 years old demonstrated efficacy when the drug product was compared to its vehicle. When the data was pooled, success was achieved in 41% of patients using ASM 1% cream compared to 20.1% of patients using vehicle at 6 weeks. When the pediatric population was stratified for age, <2 years, 2-11 years, and 12-17 years, all age groups showed efficacy ($p \leq 0.003$). The safety profile for patients ages 2-17 is adequate for short term therapy, with only minimal adverse events of nasopharyngitis, cough, headache, and influenza. There was an increase in infections, particularly viral, during the one-year long term safety trial. The infections were primarily self-limited and resolved. This drug is being recommended for second line therapy primarily because of preclinical data that suggests an increased incidence of lymphomas, thyroid adenomas, and cutaneous malignancies and because of the increased incidence of infection over the long-term found in clinical studies.

Infants ages 3 months-23 months had a disproportionately higher incidence of adverse events, particularly viral infections, in both the short term (6 weeks) and long term trials (6 months). These included URIs, nasopharyngitis, gastroenteritis, influenza, otitis media, asthma, diarrhea, viral rash, lower respiratory tract infection, eye infection, pharyngitis, rhinorrhea, wheezing, hypersensitivity, toothache and irritability.

[The effect that these events may have on the developing immune system in infants is unclear.]

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The preclinical studies found an increased risk for lymphoma in the studies evaluating the oral formulation of ASM 1% cream. Preclinical studies also showed an accelerated rate of development of cutaneous malignancies in the photocarcinogenicity study. Thus, it is recommended that the sponsor conduct a registry study of pediatric patients with atopic dermatitis to address the risk of developing cutaneous or systemic malignancies in patients who have long term intermittent treatment with ASM 1% cream.

[A pregnancy registry to assess the relationship of ASM 1% cream to spontaneous abortions should be established to determine if the signal in the clinical studies is a valid one,]

unless a preclinical dermal embryofetal study is performed with continuous dermal drug exposure and found to be negative.

It is recommended that ASM 1% cream be studied in immunocompromised patients, who have atopic dermatitis, both for efficacy and safety.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Pimecrolimus cream, ASM 1% cream, is an immunosuppressant drug product that was studied in patients with atopic dermatitis. The drug is an anti-inflammatory ascomycin macrolactam derivative and is a selective inhibitor of the production and release of pro-inflammatory cytokines and mediators in T cells and mast cells. Pimecrolimus inhibits T cell activation by blocking the transcription of early cytokines. In particular, it inhibits at nanomolar concentrations interleukin-2, interferon gamma (Th1-type), interleukin-4, and interleukin-10 (Th2-type) cytokine synthesis in human T cells. In addition, pimecrolimus prevents the release of inflammatory cytokines and mediators from mast cells in vitro after stimulation by antigen/IgE.¹

Since atopic dermatitis is primarily a pediatric disease, the important trials for efficacy were conducted in pediatric patients. The primary data set for evaluating efficacy in this NDA for ASM 1% cream was derived from three phase 3 multicenter double-blind, randomized, vehicle controlled clinical trials that had an intent-to-treat (ITT) population of 589 pediatric (B305, B307, and B316). There were 390 patients treated with ASM 1% cream and 199 subjects treated with vehicle. Two of these trials, B305 and B307, were US trials that included 403 pediatric subjects between the ages of 2 and 17 years of age. The third trial, B316, was a foreign trial that included 186 infants between the ages of 3 months and 23 months.

The studies that were reviewed in detail for safety include the three pivotal efficacy studies, B305, B307, and B316, each which had a 6-week double-blind phase and a 20-week open-label phase; study B313, a 1 year safety study; and study B308, a 1 year safety study in adults. Study 0315, a 6-month interim analysis, of infants was also reviewed for safety. In these trials a total of 1554 patients were treated with ASM 1% cream, 1226 pediatric patients and 328 adults. Five hundred and seventeen pediatric patients were treated with vehicle and 330 adult patients were treated with active control (a mid-potency topical corticosteroid).

B. Efficacy

The primary endpoint for treatment success in the 3 pivotal trials of atopic dermatitis with ASM 1% cream was defined as an Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) in the ITT population at day 43 (end of 6 weeks). Almost clear on the IGA scale was defined as "just perceptible erythema and just perceptible papulation/infiltration" of the skin. In trials B305 and B307 (ages 2-17), 247 out of the 403 subjects (61.3%) had a %TBSA of \geq 15% reflecting a majority of patients with at least moderate body surface area involvement. The majority of patients also accounted for mild to moderate disease activity as denoted by the Investigator's Global Assessment with 30.5% entering the study with mild disease and 59.3% entering with moderate disease activity. In the infant study, all of the infants randomized in the study had mild to moderate disease activity, with the majority, 67.2% having moderate disease

activity. A majority of the subjects (83.9%) also had a % TBSA involvement of $\geq 15\%$, reflecting a moderate body surface area of disease activity.

Two of the three studies, B305 and B316, demonstrated a statistical superiority for ASM 1% cream over its vehicle ($p=0.002$ and $p<0.001$, respectively). Study B307 was supportive in that it was numerically superior to vehicle at day 43 (32.1% vs. 20.6%) and approached significance ($p=0.076$). When the 3 studies are pooled, statistical superiority is achieved at day 43 ($p<0.001$), as 160 patients (41%) on ASM 1% cream achieved success compared to only 40 (20.1%) on vehicle.

Secondary variables that were evaluated to support the primary efficacy analysis were the signs and symptom of atopic dermatitis. These included erythema, induration/papulation, excoriation, lichenification, and pruritus. All of the secondary variables evaluated for being absent and/or mildly present in the ASM 1% cream arm were either numerically or statistically superior to those in the vehicle arm at day 43 across all three studies. Erythema, induration/papulation, and pruritus deserve special attention, as these parameters are associated with acute atopic dermatitis (although pruritus can be severe in untreated chronic atopic dermatitis).

More than half of the patients in all three studies entered with moderate to severe pruritus. At day 43, the absence of pruritus or absence to mild pruritus was statistically significant for the ASM 1% cream arm as compared to vehicle ($p\leq 0.019$). Further, by day 15 for all three studies, more patients in the ASM 1% cream arm had absent or only mild pruritus as compared to vehicle ($p<0.001$). The same can be said for the absence of or only mildly present erythema and induration/papulation. Induration/papulation was only numerically better at day 43 in study B307 but this is still supportive of the efficacy of ASM 1% cream.

An integrated subgroup analysis was performed for the three pivotal studies, B305, B307, and B316. Parameters analyzed to be discussed here include age, influence of area affected (%TBSA), and influence of baseline disease severity. IGA treatment success by endpoint was statistically significant for all age groups, <2 years ($p<0.001$), $2-<12$ years ($p<0.003$) and $12-<18$ years ($p=0.033$). ASM 1% cream was statistically significantly better in all subgroups of body surface area involved except where %TBSA was $>60\%$ ($p=1.000$). ASM 1% cream was statistically significantly better than vehicle in the subgroups where the baseline IGA was equal to 2 and 3 ($p\leq 0.12$) but not in the subgroup of patients with an IGA equal to 4 or 5 ($p=0.287$).

In summary, the data supports the efficacy of ASM 1% cream in the treatment of mild to moderate atopic dermatitis where the total body surface area of involvement is not greater than 60% for up to 6 weeks. The natural history of the disease process is the same for adults as it is for the pediatric population, with the sites of predilection of adults mirroring that of the older child. Therefore, efficacy can be extrapolated upward to include the adult population, even though no placebo controlled trial was performed in this population.

The one adult study should be mentioned briefly, primarily as it was intended as a safety study. It was a head to head comparison of ASM 1% cream with a mid-potency topical corticosteroid (triamcinolone acetonide cream, 0.1%). The patients used a low potency topical corticosteroid (hydrocortisone acetate cream, 1%) for the face and intertriginous areas). At each evaluation time point, the topical corticosteroid subjects had a statistically significant better response ($p<0.001$) than did those treated with ASM 1% cream. The majority of these patients, unlike the pediatric patients, had moderate to severe disease, which may have accounted for this outcome.

C. Safety

The studies that were reviewed in detail for safety include the three pivotal efficacy studies, B305, B307, and B316, each which had a 6-week double-blind phase and a 20-week open-label phase; study B313, a 1 year safety study; and study B308, a 1 year safety study in adults. Study 0315, a 6-month interim analysis, of infants was also reviewed for safety. In these trials a total of 1554 patients were treated with ASM 1% cream, 1226 pediatric patients and 328 adults. Five hundred and seventeen pediatric patients were treated with vehicle and 330 adult patients were treated with active control (a mid-potency topical corticosteroid).

The mean duration of treatment for subjects ages 2-17 years in the 6 week phase was 39.3 days for ASM 1% cream and 35.2 days for vehicle. In the infant trial of the same duration, the mean treatment days was 27.2 days for ASM 1% cream and 31.0 days for vehicle. The open-label phases of these trials the mean number of treatment days was 112.1 for subjects ages 2-17 years and 96.2 days for infants. For pediatric patients ages 2-17 years in the long-term (1 year) study, the mean number of treatment days for subjects on ASM 1% cream was 205 days. The median number of treatment days for the 6 month interim analysis of infants was not much different from the open-label phase of the pivotal trial, 94.5 treatment days. The infant data base is incomplete but enough data could be analyzed to come to a safety conclusion in this age group. Patients were adequately monitored throughout the trials.

Infection was a recurrent theme in the safety analysis of ASM 1% cream, especially viral infections. Infants treated with ASM 1% cream had a clinically significant higher incidence of infections and adverse events than did their counterparts treated with vehicle in the double-blind studies, both short term (6 weeks) and long term study (6 months). The number of infants with adverse events on ASM 1% cream in the double-blind phase of the pivotal trial approached significance ($p=0.052$) when compared to vehicle. This reflected a higher incidence of systemic infections in this population. Infants suffered from a disproportionately higher incidence of URIs, nasopharyngitis, gastroenteritis, influenza, otitis media, asthma, teething, and diarrhea. The markedly increase incidence of pyrexia (31.7 % vs. 12.7%) in infants on ASM 1% cream reflects this apparent increase susceptibility to infection in infants on ASM 1% cream. The open-label phase of the short-term trial further illustrates this concern of infection in infants. Not only did the incidence of some infections rise in the infants who had been on ASM 1% cream in the double-blind phase but infants who had been on vehicle began to experience the same increases in infection when placed on ASM 1% cream. Their incidence of URIs, nasopharyngitis, otitis media, gastroenteritis, diarrhea, and teething, either almost equaled or surpassed the incidence in the original ASM 1% cream patients. Other infections that began to emerge were those such as bronchitis, tonsillitis, bacterial infection, ear infection, molluscum contagiosum, chickenpox, pneumonia, croup infectious, an increase in cough symptoms, bronchospasm, vomiting, contact dermatitis, conjunctivitis, and hypersensitivity. When compared to vehicle in the long-term study, many of these infections/disorders continued with many occurring at an incidence rate of $>2\%$ over vehicle and others becoming statistically significant and including viral rash, lower respiratory tract infection, eye infection, pharyngitis, respiratory tract infection, rhinorrhea, wheezing, toothache, hypersensitivity, and irritability.

In those short-term studies of 3 weeks duration, infants (<2 years of age) had more URIs and flu like symptoms than did children between the ages of 2-14 years, 37% and 15%,

respectively. Thus, the increase skin surface area to body mass ratio in infants may be responsible for the increased absorption and thus the overall poor safety profile observed.

The majority of the adverse events in the pivotal trials of pediatric patients, ages 2-17 years of age, were reported as mild to moderate (>95%). There were only small differences in adverse events between subjects on ASM 1% cream and vehicle in the short term (treatment up to 6 weeks). The events that had a 1-3% difference in incidence rate between ASM 1% cream and vehicle were nasopharyngitis, influenza, otitis media, nasal congestion, and URIs. The two exceptions to this difference in incidence were headache, which had a 5.1% difference and cough, which had a 3.5% difference. In the long-term safety study over 1 year, the difference in the incidence of these adverse events, nasopharyngitis, influenza, cough, and headache, between ASM 1% cream and vehicle rises. More types of infections occur over the course of 1 year, particularly viral (e.g. bronchitis, pharyngitis, gastroenteritis). Viral infections of the skin that began to emerge by the 1 year mark included skin papilloma (warts), molluscum contagiosum, herpes simplex dermatitis (eczema herpeticum), and herpes zoster. The incidence of herpes diseases were not overall increased in the ASM 1% cream subjects. These infections (herpes) did not become disseminated and resolved with appropriate therapy. There were not any instances of isolated lymphadenopathy. All instances of lymphadenopathy were associated with infection and resolved. There were not any laboratory abnormalities that could be attributed to ASM 1% cream. One parameter, skin anergy testing, revealed that cellular immunity is not totally depressed by use of ASM 1% cream. Finally, using a mid-potency topical corticosteroid sequentially with ASM 1% cream did not significantly increase the incidence of systemic infection in this age group. Increases were observed primarily in skin infections and included impetigo, other skin infection, and superinfection. Exceptions to this were an increase in rhinitis (without a concomitant increase in nasopharyngitis) and urticaria.

One parameter outside the realm of infection that occurred with a high incidence was that of headache. In the one-year safety study, 25.4% of patients on ASM 1% cream had this complaint compared to 16.0% of patients on vehicle.

It is the opinion of this reviewer that the safety profile observed in pediatric patients ages 2-17 in the short-term is adequate to allow the use of ASM 1% cream to be used in the treatment of mild to moderate atopic dermatitis up to 6 weeks. There was not a large difference between ASM 1% cream and vehicle in the incidence of infection in the short term, suggesting that the immune system of this age group is not overly compromised by the immunosuppressant activity of this drug product.

However, in the long term, the incidence of infection increases, even with intermittent use. Therefore, appropriate precautions need to be in place to decrease any morbidity that may occur as the result of using ASM 1% cream in the long term. Physicians should be advised that the drug product should be discontinued if the disease process resolves earlier than 6 weeks. Physicians, especially those that are not primary care physicians, should be vigilant for infections that may be attributable to the drug product and use clinical judgement concerning drug interruption. Although lymphadenopathy was primarily associated with infection and resolved, physicians must be made aware to check for it and any lymphadenopathy that does not resolve must be evaluated further. In an attempt to decrease the incidence of these infections in children,

ASM 1% cream may need to be cycled during the year with a drug product of a different class (with a different mechanism of action), for any relapses of atopic dermatitis if used as first line therapy. Otherwise, use as a second-line therapy in the treatment of atopic dermatitis may be more appropriate.

The incidence of acute infection in adults in the long term study was overall lower than in the pediatric population.

Given that atopic dermatitis is a remitting and relapsing disease, the duration of exposure for the time periods assessed is adequate to assess acute events, such as infection. However, preclinical data suggests a possible risk for the development of lymphoma and cutaneous malignancies. The risk in the human population could not be completely assessed over such a short time period. In the trial of 328 adults who were on ASM 1% cream over the course of a year, no patient developed a malignancy. One patient developed a benign ovarian tumor and was found to be HIV positive. This data suggests that at least for adults, the risk is not immediate but it does not address the long-term use of ASM 1% cream, especially in the pediatric population.

Populations that were excluded that may be of some concern if they were to use ASM 1% cream are immunocompromised subjects, subjects with a history of malignancy, especially cutaneous malignancy where the risk of a new occurrence is increased, and those subjects who had been treated within one month of the study entry with the following drugs or drug therapy: phototherapy, immunosuppressants, cytostatics, systemic corticosteroid, or leukotriene antagonists. It is recommended that because immunocompromised patients were not studied, they should not be included in the indication. For the drugs and drug therapy issues, these drugs should not be used within one month of those particular therapies as the interaction and/or additive effect with ASM 1% cream has not been studied. Caution should be exercised with patients with a history of cutaneous malignancy in the use of ASM 1% cream.

D. Dosing

Use of ASM 1% cream is being recommended to be applied to diseased skin of patients bid for up to 6 weeks. The drug product should be discontinued if resolution is achieved at an earlier time point. The dosing regimen as it applies to atopic dermatitis has been discussed under the safety section and the reader is referred to that section.

E. Special Populations

Gender differences were not discerned for efficacy in use of ASM 1% cream. It was statistically significant in efficacy for both males ($p=0.002$) and females ($p=0.033$). ASM 1% cream was statistically significantly better than vehicle in both White ($p<0.001$) and non-White groups ($p<0.001$). There were not enough patients in individual ethnic groups to look at each individually, thus the analysis was performed on Whites and non-Whites.

The pharmacologist/toxicologist, Dr. Hill, is recommending that ASM 1% cream have a pregnancy C category. Embryotoxic effects were seen in the oral rat studies at significant systemic exposure. This could be a potential teratogenic signal for ASM 1% cream. The spontaneous abortion rate in the studies was 33% but the numbers were very small and a definitive conclusion from this limited data cannot be made.

3 Regulatory Background

3.1 Previous FDA Actions

Agency response to phase 3 protocols: 2/11/99, 8/31/99, 2/08/00

3.2 FDA/Applicant Meetings

PreIND meeting date: 5/12/97

End-of-phase 2 (EOP2) meeting dates: 10/26/98 & 11/23/98 – The following is a summary of recommendations made by the division regarding the phase 3 studies taken from the minutes of the above EOP2 meeting dates:

The primary efficacy endpoint for the pivotal studies would be “Investigator’s Global Assessment”.

The assessment should be static

There should be a multi-level scale with discrete levels

Each level of the scale should have morphological descriptions

The morphological scale should incorporate clinical signs such as:

erythema, papulations/edema, erosion/oozing/crusting, lichenification

The Investigator’s Global Assessment should support the dichotomized analysis (success or failure)

There does not have to be complete clearing for a successful outcome (unlike an infection).

Evaluation of multiple target sites is acceptable.

Establishing the safety of ASM 981 for chronic use (beyond the 6 months recommended in the ICH-E1A guideline) is recommended.

PreNDA meeting date: 5/8/00

4 Material Reviewed

Original submission: Volumes 1.1, 1.2, 1.141-1.143, 1.148, 1.154-1.186, 1.205-1.228; 1.291-1.298, 1.310

120-day Safety Update (submitted 5/2/01): Volumes 3.1-3.81

Clinical Amendment (submitted 5/25/01): Volumes 5.1-5.74

Information Request (submitted 9/12/01): Volumes 9.1-9.12

5 Chemistry/Manufacturing Controls

No manufacturing and control problems of any clinical significance have been identified in consultation with the reviewing chemist (see chemistry review).

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6 Animal Pharmacology/Toxicology

The following statements are a brief summation of preclinical effects taken from the pharmacology/toxicology review. Please refer to the pharm/tox review for complete details of the preclinical effects of the drug product, ASM 981 oral and dermal formulations.

Reduced lymphocyte counts and atrophy of the thymus cortex was noted in the 13 week oral toxicity study in mice at ≥ 50 mg/kg. At higher doses, lymphomas were seen in the spleen, mesenteric lymph nodes, and thymus; islet cell vacuolation and slight increases in serum glucose; alteration of cycle-related histomorphological changes in the vagina associated with uterine atrophy; and reductions in serum magnesium. Reduced lymphocyte counts and medullary atrophy of the thymus were also seen in the rat along with reductions in serum magnesium and inflammatory cell infiltration and edema noted in the glandular stomach. All of these effects were secondary to the immunosuppressive properties of ASM 981. Direct toxicologic effects seen in the rat included functional and morphological changes in the kidney, pancreas, lens of the eye, prostate gland, vagina, and uterus. Potential target organs of toxicity identified in the 26-week oral toxicity study in minipigs included the arteries, adrenals and lungs.

No systemic toxicity was noted in the 26-week dermal toxicity study in rats. The design of the study was adequate because the 1% ASM cream is the maximum feasible concentration in the to be marketed formulation and an adequate amount of the cream was applied daily for 20 hours/day. The same can be said for the 26-week dermal toxicity study in adult minipigs and a 13-week dermal toxicity study in juvenile minipigs.

Malignant lymphoma was noted as a treatment related neoplastic lesion in the oral mouse carcinogenicity study. No signal for dermal or systemic carcinogenicity was noted in the dermal rat carcinogenicity study conducted with the final to be marketed 1% ASM 981 cream. There was also no statistically significant increase in any common tumors detected in this study. However, according to the pharmacologist, this study has an incomplete histopathological analysis. Dermal administration of ASM 981 cream to rats and rabbits during the time of organogenesis was well tolerated and did not show any indication of embryotoxic or teratogenic potential. However, the study design was suboptimal, according to the pharmacologist, as daily administration of ASM 1% cream for 24 hours would have been preferable to the 6 hours done in the studies.

Dr. Hill, the pharmacologist/toxicologist, determined from dermal carcinogenicity studies in mice that the multiple of human exposure based on the NOAEL suggested an adequate safety margin for the potential concern of lymphoma formation in humans after use of 1% ASM 981 cream under maximum use conditions. The same can be said for benign thymoma based on information for female rats but not male rats.

Finally, in the mouse photocarcinogenicity study, there was a strong signal that ASM 1% cream can potentially increase the risk of skin cancer from UV exposure in humans. There was a significant enhancement of photocarcinogenesis observed with vehicle alone and a decrease in time to skin tumor development.

In summary, the data suggests a low risk for the development of systemic end-organ damage via the dermal route of exposure to ASM 1% cream provided the degree of

absorption is low in humans. The potential for cutaneous malignancy, via interaction with UVR, appears to be increased.

7 Human Pharmacology, pharmacokinetics, pharmacodynamics

The comments from the biopharmaceutics review will be limited to a summary of the analysis of the blood concentration of ASM 1% cream and its possible relationship to clinical infection. Please refer to the biopharmaceutics review for complete details of the pharmacokinetic and pharmacodynamics of ASM 1% cream in human subjects.

There were 6 studies that evaluated the blood concentrations of ASM 1% cream. Five of the studies were for a duration of three weeks, including all the pediatric studies. One study, in adults, was for one year. The limit of quantitation (LOQ) was calculated as _____ and is equal to the lowest concentration of SDZ ASM 981 in the calibrator samples. The studies showed that a larger percentage of pediatric patients had ASM 981 blood concentrations above _____ than did adults. The percentage of pediatric patients above the LOQ ranged from 29% in one study to 75% in another. Adults had a range from 2% - 5%. In the two studies that had only subjects < 2 years of age, the percentage of subjects over the LOQ ranged from 29% to 75%. The highest C_{max} in adults was 1.4 ng/ml. In all the pediatric studies a higher C_{max} was observed than in the adult studies with the highest C_{max} observed in infants at 2.6 ng/ml.

In these studies, 13 out of 35 (37%) of infants <2 years reported upper respiratory tract and/or flu-like symptoms as opposed to 2 out of 13 (15%) of children 2-14 years old. In contrast, 13 out of 24 (25%) adults also reported similar symptoms. Out of 6 high and spurious concentrations reported in all the studies combined, 5 were found in infants.

In the biopharmaceutics review, there were no apparent differences observed among infants, children, and adults in terms of blood levels of ASM 981 and efficacy.

8 Clinical Background

8.1 Relevant human experience

This is a new chemical entity and therefore, there is not any other relevant human experience other than what will be discussed in this review.

8.2 Foreign experience

Elidel (pimecrolimus cream) Cream, 1% has not been marketed in any country outside the United States. There have been no regulatory actions regarding pimecrolimus for any reason related to safety or effectiveness.

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Labeling



Reviewer's Comment: The above sections of the label are as submitted by the sponsor and may be modified depending upon the review of the data. It is important to note that the phase 3 studies were not for all patients with atopic dermatitis but for those patients with mild to moderate disease.

10 Description of Clinical Data Sources

10.1 Clinical Studies

Study #ASMW 203 – This is a trial to determine the dermal irritation potential of 1% SDZ ASM 981 cream. This trial is a double-blind, randomized, placebo-controlled, within-subject repeated application design. It included 30 healthy adults, at a single center, of which 29 completed. The first subject enrolled January 12, 1998 and the last subject completed the trial on March 11, 1998.

Study #ASMW 201 – This is a trial to determine the contact allergic potential of 1% SDZ ASM 981 cream. It is a double-blind, randomized, placebo-controlled, with subjected repeated application design. Two hundred eleven healthy adult subjects were enrolled in the trial at a single center, of which 200 completed the study. The first subject was dosed on February 23, 1998 and the last subject completed on September 24, 1999.

Study #2301 – This is a trial to determine the phototoxic potential of 1% SDZ ASM 981 cream. It is a double-blind, randomized, placebo-controlled, within-subject single topical application study. Twenty healthy, adult subjects were enrolled at a single center in Paris, France and 20 subjects completed the trial. The first subject was dosed on August 21, 2000 and the last subject completed the study on September 7, 2000.

Study #2302 – This is a trial to evaluate the photoallergic potential of 1% SDZ ASM 981 cream. It is a double-blind, randomized, placebo-controlled, within-subject repeated topical application design. The trial enrolled 34 subjects at a single center in Paris,

France. Thirty-three subjects completed the study. The first subject was dosed on July 31, 2000 and the last subject completed September 29, 2000.

Study #ASMB 202 – This was a randomized, multicenter, double-blind vehicle-controlled parallel group trial to determine the safety and efficacy of 4 concentrations (0.05%, 0.2%, 0.6%, and 1.0%) of SDZ ASM 981 cream and 1.0% betamethasone-17-valerate cream applied twice daily for up to 3 weeks in moderate atopic dermatitis. There were 14 non-US centers: three in the Netherlands, four in Germany, two in Denmark, two in the UK and one each in Finland, Norway, and Belgium. Two hundred and sixty adult patients were randomized to this trial. The first subject was enrolled on October 7, 1997 and the last subject completed the study March 5, 1998.

The following studies were reviewed for efficacy and safety:

Study #CASB B305 – This was a 26-week study with 2 phases, a 6-week randomized, double-blind, vehicle-controlled, parallel-group trial and a 20-week open-label phase to study the safety and efficacy of 1% SDZ ASM 981 cream in pediatric patients ages 2-17 with atopic dermatitis. There were 198 subjects randomized in a 2:1 randomization to ASM 1% cream and its vehicle (130 to ASM 1% treatment and 68 to vehicle). All subjects, except 2 on ASM 1% cream, who completed the double-blind phase entered the open-label phase. There were 11 centers, all within the continental United States. The first patient enrolled on June 29, 1999 and the last patient completed the double-blind phase March 31, 2000. The last patient completed the open-label phase August 23, 2000.

Study #CASB B307 – This was a 26-week study with 2 phases, a 6-week randomized, double-blind, vehicle-controlled, parallel group trial and a 20-week open-label phase to study the safety and efficacy of 1% SDZ ASM 981 cream in pediatric patients ages 2-17 with atopic dermatitis. There were 205 subjects randomized in a 2:1 randomization to ASM 1% cream and its vehicle (137 to ASM 1% treatment and 68 to vehicle). All subjects, except 2 on ASM 1% Cream who completed the double-blind phase entered the open-label phase. There were 11 centers, all within the continental United States. The first patient enrolled on June 22, 1999 and the last patient completed the double blind phase of the study on March 30, 2000. The last patient completed the open-label phase on August 17, 2000. The interim report cut-off was June 15, 2000.

Study #CASB 981 0316 – This was a 26-week study with 2 phases, a 6-week randomized, double-blind, vehicle-controlled, parallel group trial and a 20-week open-label phase to study the safety and efficacy of 1% SDZ ASM 981 cream in pediatric patients ages 3 months – 23 months with atopic dermatitis. There were 186 patients randomized in a 2:1 randomization to ASM 1% cream and its vehicle (123 to ASM 1% treatment and 63 to vehicle). There were 25 centers which enrolled subjects, one in Australia, four in Brazil, four in Canada, five in Germany, seven in South Africa, and four in Spain. The first patient enrolled on April 5, 2000 and the last patient completed the open-label phase on January 9, 2001.

The following studies were reviewed for safety:

Study #ASMB 313 – This was a 12 month double-blind vehicle-controlled trial to study the efficacy and safety of ASM 981 1% cream in the long term management of atopic

dermatitis in children ages 2 to <18 years. Seven hundred and thirteen patients were randomized in a 2:1 randomization. Four hundred and seventy-four subjects received the pimecrolimus treatment paradigm (emollients, ASM cream, medium potency topical corticosteroids) and 237 subjects received standard of care (emollients, vehicle, medium potency topical corticosteroids). There were 53 center in which 52 centers randomized subjects and all centers but one was a non-US center. These included one in Austria, two in Australia, four in Canada, one in Switzerland, two in the Czech Republic, 8 in Germany, seven in France, 4 in the UK, four in Hungary, 3 in Italy, seven in the Netherlands, 9 in South Africa, and 1 in the United States. The first patient enrolled on July 5, 1999 and the last patients completed on December 13, 2000.

Study #ASMB 315 – This was a 12 month double-blind vehicle-controlled trial to study the efficacy and safety of ASM 981 1% cream in the long term management of atopic dermatitis in infants ages 3 months – 23 months old. This study protocol is identical to that of trial B313. This was a multicenter, foreign trial in which 39 centers randomized subjects. There was one center in Belgium, 4 in Canada, 7 in Germany, 5 in France, 2 in New Zealand, 7 in South Africa, 1 in Spain, and 14 in the UK. Two hundred and fifty-one subjects were randomized and 250 were analyzed (204 on ASM 1% cream and 46 on vehicle). The first patient was enrolled on February 17, 2000 and the last patient completed (at 6 months) on January 17, 2001. This trial was not reviewed in detail, as only a 6-month interim analysis was submitted, which covers the same time period as the pivotal trial (double-blind plus open-label phases), but the summary table of common adverse events is used as supportive of this reviewer’s position.

Study #B308 – This was a 12-month multicenter, parallel group, double-blind, active controlled study to evaluate the long-term safety of SDZ ASM 981 cream applied twice daily for up to 12 months in **adult** subjects with atopic dermatitis. Six hundred and fifty eight subjects were randomized 1:1, 328 in the ASM 1% cream arm and 330 in the control arm [triamcinolone acetonide cream 0.1% (hydrocortisone acetate cream 1% for face, neck and intertriginous areas)]. There were 35 non-US centers that participated in the study. Three in Belgium, 5 in Canada, 2 in Denmark, 1 in Finland, 7 in France, 6 in Germany, 3 in The Netherlands, 3 in Norway, and 5 in the United Kingdom. The first patient enrolled on March 30, 1998 and the last patient completed on March 9, 2000.

11 Clinical Studies

11.1 Dermal Toxicity Studies

11.1.1 ASMW 203-E-00/001 – “A Study on the Cumulative Irritation Potential of the Final Market Form of SDZ ASM 981 Cream when Administered to the Skin in Healthy Male and Female Subjects”

The objective of this study was to investigate the cumulative irritation potential of the final market form of SDZ ASM 981 cream when administered to the skin in healthy male and female subjects. The study utilized three different strengths of ASM 981 cream (0.2%, 0.6%, and 1.0%) and its vehicle without active drug. These were evaluated

simultaneously in each subject, together with a positive control, calcipotriol, 0.005% ointment and a negative control, vaseline. In addition, sodium-lauryl-sulfate (SLS) in four different strengths (0.2%, 0.4%, 0.8%, and 1.0%) and trans-retinoic acid (TRA) 0.025% were evaluated concomitantly.

This was a single-center study that was administered in a double-blind, randomized, placebo-controlled, within-subject repeated application design. It consisted of a 1-day to 2-week screening period, a 3-week treatment period and a completion evaluation at 7 days after the last application. Subjects visited the center on an ambulatory basis in the morning on the days of application and evaluation. Thirty healthy Caucasian adults between the ages of 18 and 60 were enrolled in the study, however one patient withdrew due to personal reasons.

The various test materials were applied onto the skin of the back under occlusion, using the Finn-chamber technique. Patches remained in place for 24 hours, except during the weekends, where the patches were removed after 72 hours. A total of 15 repeated topical applications of the various test materials was performed on the same sites over 3 weeks. The results are listed in table 1.

Table 1
Frequency of Individual Maximal Scores
and Overall Total Sum of Scores (Day 2 to 22)

Test Product/Score	0	0.5	1	2	4	TS
SDZ ASM 981 0.2% cream	11	12	6	1	0	48.5
SDZ ASM 981 0.6% cream	7	16	5	2	0	52
SDZ ASM 981 1.0% cream	11	13	5	1	0	51
Vehicle (placebo)	11	13	6	0	0	51
Calcipotriol 0.005%	6	14	9	0	1	132
Vaseline	20	8	2	0	0	12.5
SLS 0.2%	1	0	3	9	17	777.5
SLS 0.4%	0	1	0	1	28	1346.5
SLS 0.8%	0	0	0	0	30	1607
SLS 1.0%	0	0	0	0	30	1613
TRA 0.025%	1	2	10	11	6	298

The majority of the 30 subjects had no visible reaction (score "0") or faint minimal erythema (score "0.5") on test sites treated with SDZ ASM 981 0.2%, 0.6%, 1.0% creams or the vehicle. Mild and transient erythema (score "1") was observed in only 6 subjects with the same creams. Isolated occurrences of intense erythema (score "2") were observed in one subject on sites treated with SDZ ASM 981 0.2% and 1.0% cream and in two subjects on sites treated with SDZ ASM 981 0.6% cream. No severe reactions (scores > "2") were observed during the study with these creams. For sites treated with calcipotriol 0.005%, the majority of the subjects presented faint minimal and mild erythema reactions. On one subject who presented a severe reaction (score "4"), the application of calcipotriol was discontinued. No subjects complained of pruritus during the study.

Generally, for sites treated with SDZ ASM 981 cream at different strengths or the vehicle, the highest total sum of scores per day was observed between days 4 and 8.

Thereafter, a decline in the susceptibility of the subjects was observed, indicating the absence of a cumulative irritant potential for SDZ ASM 981 cream at different strengths and the vehicle. An increase of the strength of SDZ ASM 981 cream did not lead to an increase in skin reactions as reflected by comparable total sum of scores of all assessments, which were between 48.5 to 52 for all formulations.

The analysis of variance of the total sum of scores (Tukey test) comparing SDZ ASM 981 cream 1.0% cream, the vehicle, calcipotriol 0.005% and vaseline showed a statistically significantly higher irritation score for calcipotriol 0.005% compared to SDZ ASM 981 1.0% cream ($p=0.036$), the vehicle ($p=0.028$), and vaseline ($p=0.0004$). No statistically significant differences were detected between the SDZ ASM 981 1.0% cream and its vehicle or vaseline.

In conclusion, no cumulative irritation potential was observed for the 0.2%, 0.6%, and 1.0% SDZ ASM 981 cream or the vehicle as compared to calcipotriol 0.005%.

11.1.2 ASMW 201 – “A Study on the Contact Sensitizing Potential of the Final Market Form of SDZ ASM 981 Cream When Administered to Skin in Healthy Male and Female Subjects”

The objective of this study was to investigate the cumulative irritation potential of the final market form of SDZ ASM 981 cream when administered to the skin in healthy male and female subjects. The study utilized three different strengths of ASM 981 cream (0.2%, 0.6%, and 1.0%) and its vehicle without active drug.

The study was a single-center, double-blind, randomized, placebo-controlled, within-subject study in which 211 patients were enrolled and 200 subjects completed the study. The study consisted of a one-day to 2-week screening period, an induction phase of 3 weeks, followed by a rest phase of 2 weeks, and a subsequent challenge application. This was followed by a completion evaluation within 7 days after the last application of study drug.

The induction phase consisted of 9 total repeated topical applications of the four test materials 3 times a week for 3 weeks to the same sight. Patches remained in place for 48 hours except on Fridays where they remained in place for 72 hours. The rest phase was 2 weeks in which no application of test material was applied. The challenge phase consisted of applying a single application of test materials on Day 36 to a site different from the sites used in the induction phase.

The amount of SDZ ASM 981 applied per two days in each individual was 0.9 mg. The maximum total amount applied was 9 mg during the entire study.

The sites of application were scored on day 1, before the first application of the test materials, and 30 minutes after removal of the patches up to day 22 during the induction phase and 48 h, 72 h, and 96 h after the challenge application. The following scoring scale was used for the study:

0 = no visible reaction

0.5 = faint, minimal erythema

- 1 = erythema
- 2 = intense erythema
- 3 = erythema, induration and vesicles
- 4 = severe reaction with erythema, induration, vesicles, pustules

The following qualitative criteria would have been added to the score when appropriate:

- E = additional edema
- D = chaps and desquamation

The results of this study are as follows:

A total of 211 subjects, 69 males and 142 females, aged 18-59 years (mean 31.5 years), of whom 208 were Caucasian, 1 was Oriental, and 2 were classified as "Other" were included in the study. From the 11 subjects who discontinued the study prematurely, five subjects withdrew due to adverse events not suspected to be related to the study medication or because they required a concomitant medication during the study not allowed. Another 6 subjects discontinued the study due to personal reasons. For three of the volunteers who did not complete the study, the end of study evaluation was not performed.

Reviewer's Comment: Adverse events reviewed, and this reviewer would agree that none appear to be related to active.

During the induction phase, most of the subjects presented scores of "0" (no visible reaction, 50-60% of the subjects), "0.5" (faint minimal erythema, 30-40%), and "1" (erythema, 10-15%). One – two percent of patients presented with a score of "2" (intense erythema). None of the subjects presented with a score above "2". Generally, the total sum of scores of all subjects per day was lowest on Day 3 and reached a maximum on day 5 or 8, but declined after repeated applications to values observed on day 3. The daily total scores sums were slightly lower on sites where placebo had been applied.

During the challenge phase the majority of patients presented with no visible reaction after the challenge application. After 24 hours, the majority of patients had erythema scored "0" or "0.5" for all test sites. Two subjects for the 0.6% and the 1% SDZ ASM 981 cream presented an erythema reaction scored 2. However, in all these subjects, the intensity of the reactions decreased to score 0 after 48 and 72 hours, with the exception of one subject who presented a score "1" after 48 hours on the 0.2% formulation. No skin reactions above 2 were recorded.

No patients complained of itching or pruritus throughout the study. There were also not any clinically significant variations in laboratory parameters, vital signs, or physical examination.

Reviewer's Comment: The induction phase of this study is consistent with the results of the cumulative irritancy study, a low cumulative irritancy potential. The results of the induction phase indicate that contact sensitization for SDZ ASM 981 1% cream is unlikely to be a clinically significant factor for its proposed use.

11.1.3 “A Study on the Phototoxic Potential of 1% SDZ ASM 981 Market Formulation Cream When Administered to the Skin of Healthy Subjects”

Study Design/Plan

This study was a single center, double-blind, randomized, placebo-controlled, within-subject single topical application study. Products that were tested were ASM 1% cream and its vehicle. A blank chamber was also used as a non-treated control. Prior to test product applications, the M.E.D. of U.V. (A+B) was determined in each patient.

On day 1, ASM 1% cream, its vehicle and the blank control were applied under occlusive setting for 24 hours on the back, three to each side. After removal of the patches (day 2), one set of test sites was irradiated with 20 j/cm² of UVA, followed by 0.8 M.E.D. of U.V. (A+B).

All sites were evaluated and scored for possible skin erythema reactions prior to test product application, 15-30 minutes after removal of the patches, and 10 minutes, 24 hours, and 48 hours after irradiation. The grading scale ranged from 0, no reaction to 3, severe erythema reaction (see scale below under section 11.1.4). A phototoxic compound would produce either a wheal-and-flare response immediately after UV exposure, or intense erythema and edema 24 or 48 hours later.

Study Results

Twenty healthy adult male and female Caucasian subjects with skin types I-III enrolled and completed the study. No visible erythematous reactions (score 0) were recorded 10 minutes after irradiation. On day 3, 24 hours after irradiation, minimal to moderate erythema (scores 0.5 to 2) were observed irrespective of treatment (SDZ ASM 981 1% cream, vehicle, blank patch). At inspection on day 4, 48 hours after irradiation, these erythema reactions had cleared (score 0) in most subjects or reduced to minimal or mild erythema (score 0.5 to 1). Hyperpigmentation was noted 10 minutes after irradiation and at all following inspections in almost all subjects. At non-irradiated sites no erythema reactions or other local skin reactions were observed irrespective of treatment.

Reviewer's Comment: This study demonstrated a normal physiologic response to UV irradiation and did not demonstrate any phototoxic potential of SDZ ASM 981 1% cream.

11.1.4 “A Study on the Photoallergic Potential of 1% SZA ASM 981 Market Formulation Cream When Administered to the Skin of Healthy Subjects”

Study Design/Plan:

This study was a double-blind, single-center, randomized, placebo-controlled, within-subject repeated topical application study in which 34 patients enrolled and 33 completed the study. Its design was based on the photomaximization testing of Kaidbey and Kligman. The 1% SDZ ASM 981 market formulation cream, and the placebo cream were tested simultaneously in each subject under Finn-chamber patch tests. A blank (empty) one was used as a non-treated control.

Prior to product application, the M.E.D. of U.V. (A+B) were determined in each patient. The study occurred in three phases: an induction phase, a rest phase, and a challenge phase. The induction phase consisted of applying ASM981 cream, its vehicle, and the blank control to the same site twice weekly for 3 weeks. After removal of the patches, 24 hours after application, each test site was irradiated with 2 M.E.D. of U.V. (A+B) during the first week and with 3 M.E.D. during the second and third week. No applications were applied and nor irradiation given during the two-week rest phase. On day 36, the end of the rest phase, the challenge phase consisted of a single 24-hour topical application of the same test products under occlusive conditions, in duplicate, on naïve sites. After removal, one set of test sites was irradiated with 0.8 M.E.D. of U.V. (A+B) followed by 10J/cm² of UVA. The other set of test sites was not irradiated (non-irradiated control).

The sites were scored prior to test product application (days 1, 8, 15, 36), 15-30 minutes after removal of the patches (days 2, 4, 9, 11, 6,18, 37) and 24 hours (days 3, 5, 10, 12, 17, 19, 38) 48 hours (day 39), and 72 hours(day 40) after the end of irradiation for possible skin erythema reactions using the following scale:

0	=	no erythema (normal skin)
0.5	=	erythema barely visible
1	=	mild erythema
2	=	moderate erythema
3	=	severe erythema

Other local reactions were noted and recorded.

Study Results

All subjects developed erythema reactions (score 0.5 to 3) during the induction phase. In each subject almost the same skin reaction pattern was observed, irrespective of treatment. At challenge, the majority of test sites showed either no or only barely visible erythema (score 0 to 0.5), while some subjects developed mild erythema (score 1). For each subject, at the respective evaluation, the scores of skin reactions for the sites treated either with SDZ ASM 1% cream or its vehicle were identical to the scores of the untreated sites. Thus, these reactions were a physiologic reaction to the irradiation and not to the ASM 1% cream.

Reviewer's Comment: *The results did not reveal any photoallergic potential of SDZ ASM 981 cream that would preclude its clinical use for the proposed indication.*

11.2 Sponsor's protocol #ASMB 202-E-00

Title: “A randomized, multicenter, double-blind vehicle-controlled parallel group trial to determine the safety and efficacy of 4 concentrations (0.05%, 0.2%, 0.6%, and 1.0%) of SDZ ASM 981 cream and 1.0% betamethasone-17-valerate cream applied twice daily for up to 3 weeks in moderate atopic dermatitis”

Summary: There were 260 patients randomized to in approximately equal numbers to the six arm study of vehicle, 0.05% ASM, 0.2% ASM, 0.6% ASM, 1.0% ASM, and 1.0% betamethasone-17-valerate (BMV) cream. Patients applied the medication twice daily for three weeks. The primary efficacy variable was based on the Hanifin score for severity of dermatitis endpoint. The results demonstrated that the median Hanifin score decreased in all treatment groups. SDZ ASM 981 at all concentrations other than 0.05% was associated with significantly greater decreases than vehicle, as was BMV. BMV was superior to all SDZ ASM 981 doses (see statistical review for full analysis).

There were systemic events that occurred in from 1-5% of subjects in any one group such as influenza-like illness, headache, and viral infections but only headache was reported in any one group in at least 10% of subjects (ASM 0.05% and BMV). Application site reactions (feeling of warmth, burning, stinging, smarting, etc) were the most common AE's in the ASM 981 groups, occurring in 23.9 –48.9% of subjects. In the majority of cases these were of mild to moderate severity and were transient (stopped within first 3 days of study). The other AEs reported by more than 10% of patients in any treatment group were pruritus, worsening atopic dermatitis, dry skin and skin irritation. These, along with other skin disorders, were reported in 28.6-67.4% of subjects.

Conclusion: SDZ ASM 981 cream was effective in the treatment of atopic dermatitis. A clear dose response was observed, with 0.2%, 0.6% and 1.0% ASM 981 all being superior to the vehicle cream. All ASM 981 concentrations were less effective than the high-potency topical steroid BMV. The 1.0% cream was similar to the 0.6% cream on the main efficacy parameters, but had a more rapid effect on pruritus, showed a higher rate of partial clearance and had a lower discontinuation rate due to treatment failure or worsening of dermatitis, while having a similar tolerability profile to lower concentrations. Thus, ASM 981 1% cream was selected for further development (see statistical review for full details).

11.3 Sponsor's protocol # CASM981 B305

Title: “A 26-week study with a 6-week randomized, multicenter, double-blind, vehicle-controlled, parallel-group phase followed by a 20-week open-label phase to study the safety and efficacy of 1% DZ ASM 981 cream in pediatric subjects with atopic dermatitis”

11.3.1 Financial Disclaimer: As per Form 3454, the sponsor has certified that no financial arrangements with investigators have been made where the outcome affects compensation, and that investigators have no proprietary, significant equity, interest, or any significant payments in this clinical study performed in support of this NDA.

11.3.2 Investigators

1.	John Y.M. Koo, M.D.	501/San Francisco, CA
2.	Lawrence F. Eichenfield, M.D.	502/San Diego, CA
3.	Daniel Stewart, D.O.	503/Clinton Township MI
4.	Ann W. Lucky, M.D.	504/Cincinnati, OH
5.	Jon M. Hanifin, M.D.	505/Portland, OR
6.	Mark R. Ling, M.D.	506/Newnan, GA
7.	Adelaide A. Hebert, M.D.	507/Houston, TX
8.	Alice B. Gottlieb, M.D., PhD.	508/New Brunswick, NJ
9.	Ken Washenik, M.D. PhD.	509/New York, NY
10.	Eduardo H. Tschien, M.D.	510/Albuquerque, NM
11.	Paul J. Honig, M.D.	511/Philadelphia, PA 19104

11.3.1.1 Objective/Rationale

According to the sponsor, the primary objective was:

To demonstrate superior efficacy of 1% SDZ ASM 981 cream compared to vehicle after 6 weeks double-blind treatment in pediatric subjects with mild to moderate atopic dermatitis (AD).

The secondary objectives were:

To determine safety and tolerability of 1% SDZ ASM 981 cream in pediatric subjects with AD treated for up to 26 weeks.

To evaluate the efficacy of 1% SDZ ASM 981 cream vs vehicle when treating the head and neck after 6 weeks of double-blind treatment

To monitor the continued effect of 1% SDZ ASM 981 cream in the management of AD when used uncontrolled for up to an additional 20 weeks.

To compare the Quality of Life (QoL) indices of subjects suffering from AD treated with 1% SDZ AMS 981 cream vs vehicle after 6 weeks double-blind treatment, as well as the QoL indices of the subjects' parents, where applicable.

Reviewer's Comment: The sponsor was made aware that while "Quality of Life indices" may be interesting, the Agency does not consider it a validated instrument at this time, and therefore, it may have little regulatory utility.

11.3.1.2 Design

This was a multicentered, 26-week, two-phase study to evaluate the safety and efficacy of 1% SDZ ASM 981 cream in the treatment of atopic dermatitis in subjects from 2 to 17 year of age. A 2:1 randomization was used in the 6-week double-blind, vehicle-controlled phase of the study in order to collect adequate data in the SDZ ASM 981 arm and to limit the number of subjects required to be treated with vehicle during this phase. Upon completion of the 6-week double-

blind phase or at disease clearance, whichever came first, patients subsequently entered the 20-week, open label phase to treat ongoing dermatitis and/or disease recurrence(s) with 1% ASM 981 cream as needed. If all lesions were cleared prior to 20 weeks the subjects continued to be evaluated but applied study drug only as needed. Further follow-up continued for approximately 4 weeks after completing the open-label phase to assess safety.

11.3.1.3 Protocol

A total of 198 subjects were enrolled at 11 study sites: 132 on active treatment and 66 on vehicle control). Subjects were to apply the study medication or vehicle twice a day for both phases of the study. Evaluations after day 1 (baseline) occurred on day 8, 15, 22, 29, 43, 71, 99, 141, 183, and 211 which corresponds to the beginning of weeks 2, 3, 4, 5, 7, 11, 15, 21, 27, and 31.

Key Inclusion Criteria

Subjects of any sex or race, from 2 to 17 years of age, with written consent of the subject or legal guardian.

Subjects with a clear diagnosis of AD fulfilling the diagnostic criteria of Williams that affected 5% total body surface area (TBSA) and with a baseline Investigator Global Assessment (IGA) of AD scored as 2 (mild) or 3 (moderate).

Subjects treated with a stable dose of bland emollient for at least 7 days.

Key Exclusion Criteria

Females who were pregnant, breast-feeding or of child-bearing potential not following contraception or children who were being breast-fed by women taking prohibited medications/treatments.

Subjects with any concurrent disease or treatments that could interfere with study evaluations:

Diagnosed with immunocompromised status, history of malignant disease or current skin diseases in the study area, impetigo, chicken pox, corticosteroid-induced perioral dermatitis, tinea corporis/tinea intertriginosa, recurrent active herpes simplex, head lice, scabies, or with a known hypersensitivity to ingredients in the study treatment.

Treated with phototherapy, systemic immunosuppressants, cytostatics, systemic corticosteroid, or leukotriene antagonist within 1 month, systemic antibiotics within 2 weeks, topical therapy (tar, corticosteroids) within 7 days or other investigational drugs within 8 weeks.

The stable use of bland emollients were allowed to untreated areas during the double-blind phase, or in the open-label phase to all skin surfaces after study treatment.

Procedures and Observations

Subjects received study drug for up to 26 weeks. For both phases, study medication was to be applied bid at the same time each day and at least 12 hours apart. Study drug was applied as a thin film to affected areas, including newly occurring lesions by the primary caregiver, or by the subject under the supervision of the primary caregiver. To allow for study medication absorption, gentle washing of the affected areas was allowed prior to study medication application, or at least 3 hours after application. Study drug application continued for the 6-week duration or until complete clearance of AD was evaluated as an IGA of 0. Afterward, subjects could continue to receive SDZ ASM 981 treatment bid in the 20-week, open-label phase. All lesions, including new lesions, were treated until the caregiver evaluated complete clearance or week 27 was reached. Subjects were followed for at least 4 weeks after study discontinuation to evaluate serious adverse events or ongoing adverse events that led to early discontinuation.

11.3.1.3.1 Population

The study population was comprised of pediatric subjects ages 2 years to 17 years who had mild to moderate atopic dermatitis affecting at least 5% of their total body surface area (TBSA). Subjects as young as ~~1~~ old were to be enrolled according to the original protocol but the age limit was raised to 2 years old in amendment 1 of August 17, 1999.

Reviewer's Comment: At the time of this study, the sponsor did not have adequate pK data to allow the enrollment of pediatric patients < 2 years of age.

11.3.1.3.2 Endpoints

Primary Efficacy Variable

Investigator's Global Assessment (performed at every visit)
Primary efficacy time point was at 6 weeks (day 43)

This endpoint provided a static (not compared to baseline) overall evaluation of the subject's atopic dermatitis. Subjects were to have pre-treatment and baseline scores of 2 (mild) or 3 (moderate) for study inclusion. Treatment success was defined as a score of 0 to 1 at the end of the double-blind phase (day 43).

Reviewer's Comment: The sponsor chose 6 weeks as the primary efficacy time point in which to evaluate efficacy. However, given the natural history of atopic dermatitis, in that the disease is very pruritic and the patient's response to pruritus is to excoriate, which aggravates the skin condition, one would expect to observe a degree of success prior to 6 weeks.

**APPEARS THIS WAY
ON ORIGINAL**

Table 2 presents the IGA score and descriptions.

Table 2
Investigator's Global Assessment

Score	Definition
0 =Clear	No inflammatory signs of AD
1 =Almost clear	Just perceptible erythema, and Just perceptible papulation/infiltration
2 =Mild disease	Mild erythema, and Mild papulation/infiltration
3 =Moderate disease	Moderate erythema, and Moderate papulation/infiltration
4 =Severe disease	Severe erythema, and Severe papulation/infiltration
5 =Very severe disease	Severe erythema, and Severe papulation/infiltration with Oozing/crusting

Secondary Efficacy Variables

Individual Signs Score
Erythema
Induration/Papulation
Excoriation
Lichenification
Pruritus Assessment Score

Reviewer's Comment: The individual signs score is a breakdown of the individual elements used in the EASI assessment. Assessment of these elements is a more valid reflection of actual disease activity than is the EASI score and therefore will be used as supportive data for the primary efficacy variable.

The individual signs score were assessed at each clinic visit as provided in table 3.

**APPEARS THIS WAY
ON ORIGINAL**

**Table 3
Individual Signs Score**

Erythema		(E)
0	None	
1	Mild	Faintly detectable erythema: very light pink
2	Moderate	Dull red, clearly distinguishable
3	Severe	Deep / dark red
Infiltration / Papulation		(I)
0	None	
1	Mild	Barely perceptible elevation
2	Moderate	Clearly perceptible elevation but not extensive
3	Severe	Marked and extensive elevation
Excoriations		(Ex)
0	None	
1	Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2	Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3	Severe	Many erosive or crusty lesions
Lichenification		(L)
0	None	
1	Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3	Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Overall pruritus was assessed using a score ranging from 0-3 (see Table 4). Pruritus was assessed by the primary care giver, in discussion with the subject, and concerned the intensity of overall itching/scratching in the 24 hours prior to the visit.

**Table 4
Severity of Pruritus Score**

Pruritus	
0	None
1	Mild
2	Moderate
3	Severe
	Occasional, slight itching/scratching
	Constant or intermittent itching/scratching which is not disturbing sleep
	Bothersome itching/scratching which is disturbing sleep

Skin infections could be treated with oral antibiotics (topical forms were avoided), topical or oral antifungals or antiviral therapies. Tar shampoos for scalp treatments were allowed. As a stable maintenance therapy for asthma bronchiale or allergic rhinitis, chromalin, oral antihistamines, inhaled corticosteroids, and β -antagonists were allowed. Vaccinations and leukotriene antagonists were prohibited during the 6-week, double-blind phase, but were

permitted in the open-label study phase. Vaccination required the discontinuation of treatment at the vaccination site for as long as any vaccination site reaction was evident.

Safety Measures

Safety assessments consisted of monitoring and recording all adverse events and serious adverse events, whether volunteered by the patient/guardian, discovered by investigator questioning, or detected through physical examination, laboratory test or other means. Physical examination, vital signs, and laboratory tests were to be performed at baseline, day 43 (week 7) and day 183 (week 27). All events would be recorded on the case report form whether considered related to study medication or not.

11.3.1.3.3 Statistical considerations

The intent-to-treat (ITT) population was defined as all subjects randomized, who were dispensed study medication. The safety population was defined as the same. The per protocol (PP) population was defined as all subjects in the ITT population who adhered to the protocol without any major deviations, adhered to the inclusion/exclusion criteria and did not violate the protocol in any way that effected efficacy evaluation.

The efficacy analysis is to be based on the ITT population with the last observation carried forward technique. Where missing values occurred for key efficacy tables, data presentation was repeated using observed cases only. The safety analysis is to be based on the safety population, which is all subjects randomized who received medication. See statistical review for further details.

11.3.1.4 Results

11.3.1.4.1 Populations enrolled/analyzed

The treatment groups are referred to as ASM 1% and vehicle for the double-blind phase and as ASM 1%/ASM 1% and vehicle/ASM 1% for the open-label phase or for when the two phases are combined in the text and tables.

One hundred and ninety-eight patients were enrolled and treated in the study at 11 investigational centers. The patient disposition is as shown in table 4.

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Table 4
Subject Disposition – B305

Number of subjects	ASM 1%/ASM 1% N (%)	Vehicle/ASM 1% N (%)	Total N (%)
Screened	N/A	N/A	219
Randomized	130	68	198
Treated	130 (100.0)	68 (100.0)	198 (100.0)
Completed DB phase	114 (87.7)	48 (70.6)	162 (81.8)
Entered OL phase	112 (86.2)	48 (70.6)	160 (80.8)
Completed OL phase	82 (63.1)	33 (48.5)	115 (58.1)
Ongoing in OL phase	11 (8.5)	6 (8.8)	17 (8.6)

Denominator for percentages is the number of randomized subjects

N/A = not applicable, DB = double-blind, OL = open-label

Source: Post-text tables 7.1-3, 7.1-4 and 7.1-8

All subjects in the double-blind phase, except for 2 on ASM 1%, entered the open-label phase of the study. Subject 503/0013 did not return for the blood draw needed to enter the open-label and subject 506/00017 did not enter open-label due to lack of efficacy and starting Benadryl for pruritus.

The predominant reasons for discontinuation from the double-blind phase in the ASM 1% group was unsatisfactory therapeutic effect and lost to follow-up. The rate of discontinuation for unsatisfactory therapeutic effect was considerably higher in subjects treated with vehicle than in those treated with ASM 1% and accounts for the higher rate of discontinuation in this group. Table 5 shows the subject discontinuations in the double-blind phase.

Table 5
Subject Discontinuations – Double-blind Phase
ITT Population – B305

	ASM 1% (N=130) N (%)	Vehicle (N=68) N (%)	Total (N=198) N (%)
Completed	114 (87.7)	48 (70.6)	162 (81.8)
All discontinuations	16 (12.3)	20 (29.4)	36 (18.2)
Reason for discontinuation			
AE(s)	1 (0.8)	2 (2.9)	3 (1.5)
Unsat. therap. effect	6 (4.6)	16 (23.5)	22 (11.1)
Protocol violation	3 (2.3)	2 (2.9)	5 (2.5)
Lost to follow-up	6 (4.6)	0	6 (3.0)

Source: Post-text table 7.1-3

The predominant reason for discontinuation from the open-label phase was unsatisfactory therapeutic effect. Most of the subjects who discontinued from the open-label phase for unsatisfactory therapeutic effect had no improvement or a worsening of their disease since the

double-blind phase or had an acute flare that was not controlled with the study medication. Table 6 shows the subjects who discontinued in the open-label phase.

Table 6
Subject Discontinuations from Open-Label Phase
ITT Population – B305

	ASM 1%/ASM 1% (N=112)* N (%)	Vehicle/ASM 1% (N=48)* N (%)	Total (N=160) N (%)
Completed	82 (73.2)	33 (68.8)	115 (71.9)
Ongoing	11 (9.8)	6 (12.5)	17 (10.6)
All discontinuations	19 (17.0)	9 (18.8)	28 (17.5)
Reason for discontinuation			
AE(s)	2 (1.8)	1 (2.1)	3 (1.9)
Unsat. therap. effect	12 (10.7)	4 (8.3)	16 (10.0)
Protocol violation	1 (0.9)	0	1 (0.6)
Withdrawal of consent	1 (0.9)	2 (4.2)	3 (1.9)
Lost to follow-up	3 (2.7)	2 (4.2)	5 (3.1)

*N = number of subjects who completed double-blind phase and entered open-label phase

Source: Post-text table 7.1-4

Table 7 shows a summary of the major protocol violations during the double-blind phase of the study.

Table 7
Major Protocol Violations – Double Blind Phase
ITT Population – B305

Major protocol violations	ASM 1% (N=130)		Vehicle (N=68)		Total (N=198)	
	N	(%)	N	(%)	N	(%)
Total protocol violations	51	(39.2)	32	(47.1)	83	(41.9)
Under-compliant [†]	21	(16.2)	15	(22.1)	36	(18.2)
IGA score <2 or >3 at Baseline	19	(14.6)	12	(17.6)	31	(15.7)
< 5% TBSA involvement at Baseline	10	(7.7)	4	(5.9)	14	(7.1)
Used anti-pruritic treatment [‡]	12	(9.2)	10	(14.7)	22	(11.1)
Used topical steroids [#]	4	(3.1)	3	(4.4)	7	(3.5)
Missed more than 2 visits or had no post-Baseline assessments	3	(2.3)	1	(1.5)	4	(2.0)
Used leukotriene antagonist [#]	1	(0.8)	3	(4.4)	4	(2.0)
Used systemic steroids [#]	3	(2.3)	0	(0)	3	(1.5)

[†]Missed >10% of doses during the double-blind phase of the study

[‡]Used to treat AD during double-blind phase of study (not stable dose at Baseline)

[#]Either within 1 week (topical steroids, leukotriene antagonists) or 1 month (systemic steroids) of Baseline visit or during double-blind phase of study.

Note: a subject who had more than one major protocol violation was counted in each category.

Source: Listings 7.2-1 and 7.3-1

No subject was randomized with an IGA score <2, however 15.7% of subjects were randomized with IGA scores >3. More subjects treated with vehicle had used leukotriene antagonists or were under-compliant (missed more than 10% of doses during the double-blind phase of the study).

Reviewer's Comment: The sponsor did not include in the table the patients with < 5% TBSA involvement of disease at baseline which was a violation of the inclusion criteria where patients should have had at least 5% TBSA involved. The sponsor grouped patients at ≤ 5%, thus it was not possible to discern those that had less than 5% from those with only 5%. Therefore, the figures in the table represent the entire group of patients. Since the distribution of this particular subset of patients across the two arms does not represent a statistically significant difference (according to the biostatistician), they have been allowed to remain in the ITT population for evaluation. The sponsor was asked to list patients with <5% BSA involvement and on 9/26/01 the results were submitted and all the patients listed in the table were in violation of the protocol. Thus the table has been modified accordingly.

Table 8 shows the baseline demographics of the ITT population.

Table 8
Baseline Demographics
ITT Population – B305

Parameter	Parameter	ASM 1% (N=130)	Vehicle (N=68)	p-value
Age (years)	mean ± SD	6.9 ± 4.2	6.4 ± 4.3	0.320 [†]
	range	1 – 17	1 – 16	
	median	6.0	5.0	
Age group (years)				
	N (%)			
	<2	3 (2.3)	3 (4.4)	
	2-<12	107 (82.3)	54 (79.4)	
	12-<18	20 (15.4)	11 (16.2)	
Sex (n, %)	Male	63 (48.5)	35 (51.5)	0.765 [‡]
	Female	67 (51.5)	33 (48.5)	
Race (n, %)	Caucasian	76 (58.5)	34 (50.0)	0.690 [‡]
	Black	19 (14.6)	12 (17.6)	
	Oriental	13 (10.0)	8 (11.8)	
	Other	22 (16.9)	14 (20.6)	
Weight (kg)	mean ± SD	28.9 ± 17.90	27.9 ± 18.2	0.346 [#]
	range	11 – 118	9 -90	
Height (cm)	mean ± SD	121.4 ± 24.5	117.5 ± 25.0	0.109 [#]
	range	82 – 184	79 – 167	

[†]Wilcoxon rank sum test

[‡]Fishers exact test

[#]Van Elteren test, stratified by age category

Source: Post-text table 7.4-1, 10.4-3

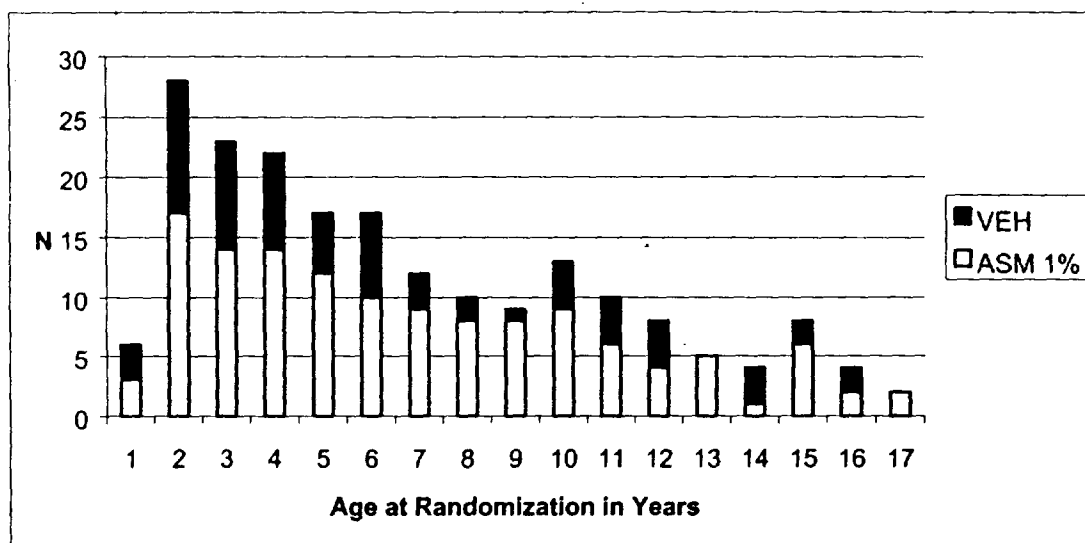
Reviewer's Comments: There were not any differences between the key demographic variables in the intent-to-treat population. A little over half the subjects in the study were Caucasian. The

remainder comprised almost 50% and are of different ethnic groups; thus having a good representation of the disease across racial groups.

Although the protocol was amended to exclude subjects <2 years old from the study until further pK data was obtained, 6 subjects had already been enrolled. After further discussion between the Agency and the sponsor, it was decided that all subjects less than 22 months would be withdrawn from the study. Thus the study does have 6 patients who fall into that category (were 22-23 months of age). However, this number is too small to draw any conclusions regarding efficacy in infants.

Figure 1 demonstrates the age distribution at randomization. The majority of subjects (81.3%) were between 2 to 12 years of age.

Figure 1
Age Distribution at Randomization
ITT Population – B305



Reviewer's Comment: The majority of patients are in the younger age range which reflects that atopic dermatitis is primarily a disease of childhood. On further analysis, 96 /198 subjects (48.5%) in the study were ≤ 5 years of age and 63% of these subjects (60 /96) were in the ASM 1% cream arm. Thus, the sponsor did meet the objective of enrolling a substantial amount of subjects in the youngest age group.

The majority of patients had moderate disease activity (IGA = 3) at baseline and two-thirds of patients had a TBSA between 6-60%. Table 9 describes the baseline disease characteristics.

**Table 9
Disease Characteristics at Baseline
ITT Population – B305**

Parameter	Parameter	ASM 1% (N=130) N (%)	Vehicle (N=68) N (%)	p-value
IGA score	2 (mild)	28 (21.5)	18 (26.5)	0.874 [†]
	3 (moderate)	83 (63.8)	38 (55.9)	
	4 (severe)	16 (12.3)	8 (11.8)	
	5 (very severe)	3 (2.3)	4 (5.9)	
% TBSA involved	<= 5%	13 (10.0)	6 (8.8)	0.598 [†]
	> 5% - <= 15%	33 (25.4)	20 (29.4)	
	> 15% - <= 30%	34 (26.2)	18 (26.5)	
	> 30% - <= 60%	30 (23.1)	17 (25.0)	
	> 60%	20 (15.4)	7 (10.3)	
		Mean ± SD range	Mean ± SD range	
% TBSA involved	overall	29.7 ± 23.3	27.4 ± 21.9	-

[†]Mantel-Haenszel Chi-square test

Source: Post-text tables 7.4-3, 7.4-4, 7.4-5 and 9.2-9

Reviewer’s Comment: *There is not a significant difference between arms in either the IGA score or % TBSA involvement. One hundred and thirty of the 198 subjects (65.7%) had a TBSA involvement of ≥ 15%. On further analysis, 70 out of 96 (73%) subjects ≤ 5 years of age had a %TBSA of ≥ 15% at baseline and 60/102 (59%) subjects ≥ 6 years of age had a %TBSA of ≥ 15% at baseline. This reflects an adequate population with moderate body surface area involvement.*

Each subject was supplied with 20 tubes of 50 g of study medication (1000 g total), with the assumption that subjects would require no more than 3 tubes per week during the double-blind phase. Two patients (501/0023 and 511/0001) from the ASM 1% group used all 20 tubes allotted for this phase and were re-supplied with 2 extra boxes (2000g) and 1 extra box (1000 g), respectively. The mean daily exposure to study medication was 38.5 days (±SD of 11.6) for the ASM 1% arm and 33.4 days (±SD 15.2) for the vehicle arm in the double-blind phase. In the open-label phase mean daily exposure was 114.4 days (±SD 42.9) for the ASM 1%/ASM 1% and 105 days (±SD50.2) for the vehicle/ASM 1% arm.

11.3.1.4.2 Efficacy endpoint outcomes

Treatment success was defined as an Investigator Global Assessment of “0” (clear) or “1” (almost clear) at day 43. There were significantly more patients with treatment success at day 43 in the ASM 1% cream arm than in vehicle. This statistical significance started as early as day 8 and was maintained weekly throughout the study. Table 10 demonstrates the results by IGA.

Table 10
Treatment Success[†] – Investigator’s Global Assessment
ITT Population – Double-blind Phase – B305

	ASM 1% (N=130)	Vehicle (N=68)	P-value [‡]
Baseline	0	0	
Day 8	19 (14.6)	1 (1.5)	0.003
Day 15	28 (21.5)	3 (4.4)	0.001
Day 22	35 (26.9)	2 (2.9)	<0.001
Day 29	46 (35.4)	4 (5.9)	<0.001
Day 43	49 (37.7)	11 (16.2)	0.002

[†]Defined as a score of 0 or 1 (clear or almost clear)

[‡]Derived from CMH test stratified by center

Source: Post-text tables 9.1-1 and 7.4-3

Table 11 shows the distribution of IGA scores by visit. There was a statistically significant difference between the treatment groups in the distribution of IGA scores at all post-baseline assessments. At endpoint, more ASM 1% subjects had an IGA score of 0 or 1. More subjects on vehicle had severe/very severe AD at endpoint compared with ASM 1%.

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Table 11
Frequency Distribution of IGA by Visit
ITT Population – B305

Visit [†]	Group	N	IGA score					p-value [‡]	
			0	1	2	3	4		5
Baseline									
	ASM 1%	130	0	0	28 (21.5)	83 (63.8)	16 (12.3)	3 (2.3)	-
	Vehicle	68	0	0	18 (26.5)	38 (55.9)	8 (11.8)	4 (5.9)	
Day 8									
	ASM 1%	130	2 (1.5)	17 (13.1)	37 (28.5)	60 (46.2)	13 (10.0)	1 (0.8)	<0.001
	Vehicle	68	0	1 (1.5)	14 (20.6)	35 (51.5)	13 (19.1)	5 (7.4)	
Day 15									
	ASM 1%	130	6 (4.6)	22 (16.9)	45 (34.6)	47 (36.2)	9 (6.9)	1 (0.8)	<0.001
	Vehicle	68	0	3 (4.4)	13 (19.1)	35 (51.5)	13 (19.1)	4 (5.9)	
Day 22									
	ASM 1%	130	8 (6.2)	27 (20.8)	44 (33.8)	42 (32.3)	8 (6.2)	1 (0.8)	<0.001
	Vehicle	68	0	2 (2.9)	17 (25.0)	32 (47.1)	13 (19.1)	4 (5.9)	
Day 29									
	ASM 1%	130	10 (7.7)	36 (27.7)	38 (29.2)	38 (29.2)	7 (5.4)	1 (0.8)	<0.001
	Vehicle	68	1 (1.5)	3 (4.4)	15 (22.1)	29 (42.6)	18 (26.5)	2 (2.9)	
Day 43									
	ASM 1%	130	13 (10.0)	36 (27.7)	32 (24.6)	38 (29.2)	9 (6.9)	2 (1.5)	<0.001
	Vehicle	68	0	11 (16.2)	11 (16.2)	29 (42.6)	15 (22.1)	2 (2.9)	

IGA categories: 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe, 5=Very Severe

[†]All non-missing post-Baseline values carried forward to all subsequent visits with missing data

[‡]CMH row mean score test, stratified by center

Source: Post-text table 9.1-2

Table 12 shows the treatment success by baseline IGA and by baseline %TBSA involved.

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Table 12
Treatment Success[†] by Baseline IGA and By Baseline %TBSA
ITT Population – B305

	ASM 1% (N=130)		Vehicle (N=68)		P-value [‡]
	N [#]	N (%)	N [#]	N (%)	
Baseline IGA					
Overall	130	49 (37.7)	68	11 (16.2)	<0.001
2	28	18 (64.3)	18	6 (33.3)	
3	83	29 (34.9)	38	5 (13.2)	
4 and 5	19	2 (10.5)	12	0 (0.0)	
Baseline %TBSA involved					
Overall	130	49 (37.7)	68	11 (16.2)	<0.001
≤ 5%	13	9 (69.2)	6	0 (0.0)	
> 5 % - ≤ 15%	33	15 (45.5)	20	6 (30.0)	
> 15% - ≤ 30%	34	17 (50.0)	18	5 (27.8)	
> 30% - ≤ 60%	30	7 (23.3)	17	0 (0.0)	
> 60%	20	1 (5.0)	7	0 (0.0)	

[†]Defined as a score of 0 or 1

[‡]Derived from CMH test stratified by Baseline factor

[#]Number of subjects assessed

Source: Post-text tables 9.1-5 and 9.1-6

Reviewer's Comment: Table 12 shows that the majority of patients who had mild atopic dermatitis responded best to ASM 981 1% cream, with 64% of the patients reported as a success. ASM 981 1% cream also worked the best in patients who had ≤ 30% total body surface area involvement. Only 2 of 19 patients with severe/very severe disease in the ASM arm were successful and none in the vehicle arm. Although there are not enough of these cases to make a statistical analysis, the drug seems least useful in patients with severe/very severe disease and also in those with > 60% total body surface area involvement.

During the open-label phase, the number of subjects clear or almost clear of disease signs by IGA score remained relatively constant for the ASM 1% group (42.9% at the end of the double-blind and 36.6% at the end of the open-label) but the number of vehicle subjects clear or almost clear doubled after treatment with ASM 1% (from 20.8% at the end of the double-blind to 45.8% at the end of the open-label phase).

Reviewer's Comment: Even though open-label studies cannot be used to determine efficacy, it is supportive in that the percentage of patients who would be defined as a treatment success that were switched to ASM 1% cream is approximately the same as the patients who were maintained on ASM 1% cream.

Secondary signs and symptoms used to support the investigator's global assessment were erythema, induration/papulation, excoriation, lichenification, and pruritus. Table 13 shows the

proportion of patients in both the double-blind and open-label phase of the study who had a score consistent with absent or mild signs for the first four signs.

Table 13
Treatment Success* – Individual Signs
ITT Population – Double-blind and Open-label Phases
B305

Visit	Treatment group	N	Erythema	Induration/ papulation	Excoriation	Lichenification
			N (%)	N (%)	N (%)	N (%)
Double-blind phase						
Baseline	ASM 1%	130	24 (18.5)	28 (21.5)	53 (40.8)	43 (33.1)
	Vehicle	68	14 (20.6)	14 (20.6)	17 (25.0)	18 (26.5)
Day 43	ASM 1%	130	74 (56.9)	70 (53.8)	70 (53.8)	68 (52.3)
	Vehicle	68	16 (23.5)	23 (33.8)	29 (42.6)	28 (41.2)
Open-label phase						
Baseline [†]	ASM 1%/ASM 1%	112	65 (58.0)	67 (59.8)	63 (56.3)	61 (54.5)
	Vehicle/ASM 1%	48	12 (25.0)	17 (35.4)	25 (52.1)	21 (43.8)
Week 27	ASM 1%/ASM 1%	112	59 (52.7)	61 (54.5)	72 (64.3)	66 (58.9)
	Vehicle/ASM 1%	48	29 (60.4)	29 (60.4)	29 (60.4)	29 (60.4)

*All body regions for the given sign with a score of 1 or less (mild or absent symptoms)

[†]Last double-blind assessment prior to entry into open-label phase

Source: Post-text tables 9.2-15 and 9.2-28

Reviewer's Comment: *The individual signs scores are supportive of the investigator's global assessment. The individuals in the ASM 1% cream had greater success at the evaluation endpoint (day 43) than did the subjects are vehicle, especially with resolution of erythema and induration/papulation. Although the open label phase cannot be used to demonstrate efficacy of a drug product, one can see that the individual signs scores remained fairly constant in those individuals that had been on ASM 1% cream throughout, while there was a significant improvement in the signs scores for patients who were switched from vehicle to ASM 1% cream.*

The severity of pruritus was assessed at each visit. A successful outcome for it was a score of 0 (absent) of 1 (mild). Table 14 delineates the pruritus assessment for the pruritus severity score at baseline, day 8, day 43 and during the open-label phase of the study.

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Table 14
Pruritus Assessment
ITT Population – B305

	Treatment group	N	0	1	2	3	p-value [†]	
			Absent N (%)	Mild N (%)	Moderate N (%)	Severe N (%)	0	0,1
Baseline	ASM 1%	130	0	22 (16.9)	55 (42.3)	53 (40.8)	0.016	0.674
	Vehicle	68	3 (4.4)	7 (10.3)	25 (36.8)	33 (48.5)		
Day 8	ASM 1%	130	10 (7.7)	50 (38.5)	41 (31.5)	29 (22.3)	0.176	<0.001
	Vehicle	68	2 (2.9)	13 (19.1)	25 (36.8)	28 (41.2)		
Day 43	ASM 1%	130	18 (13.8)	47 (36.2)	44 (33.8)	21 (16.2)	0.001	0.019
	Vehicle	68	0	22 (32.4)	18 (26.5)	28 (41.2)		
Baseline*	ASM 1%/ ASM 1%	112	17 (15.2)	45 (40.2)	37 (33.0)	13 (11.6)	N/A	N/A
	Vehicle/ ASM 1%	48	0	20 (41.7)	16 (33.3)	12 (25.0)		
Week 27	ASM 1%/ ASM 1%	112	18 (16.1)	43 (38.4)	29 (25.9)	22 (19.6)	N/A	N/A
	Vehicle/ ASM 1%	48	7 (14.6)	26 (54.2)	9 (18.8)	6 (12.5)		

[†]p-value for pruritus score of 0 (absent) or 0, 1 (absent to mild) based on CMH general association test adjusted for center

*Baseline for the open-label is last double-blind assessment prior to entry into the open-label phase

N/A = not applicable

Source: Post-text tables 9.2-29 to 9.2-32

There was no difference between the treatment groups in the severity of pruritus at baseline (p=0.644). The majority of subjects in each treatment group had moderate to severe pruritus at baseline. There were statistically significant differences between the treatment groups in the severity of pruritus at all post-baseline assessments during the double-blind phase of the study as early as day 8. Significantly more ASM 1% cream subjects had absent or mild pruritus at each visit as early as day 8 onwards.

The proportion of ASM 1% cream subjects who remained free of pruritus remained essentially constant during the open-label phase and increased markedly in the vehicle group after switching to ASM 1% cream in the open label phase by week 11 (12/48 subjects, 25%) and thereafter remained essentially constant.

Reviewer's Comment: *The pruritus severity score is supportive of the investigator's global response. One would expect in atopic dermatitis that pruritus would improve to a significant degree as the disease process resolves.*

The signs of oozing/crusting, hyperpigmentation, hypopigmentation, and xerosis were noted for presence or absence. There was not any significant difference between ASM 1% cream and vehicle for these signs, although both decreased over time from baseline to day 43 and then to week 27.

11.3.1.4.3 Conclusions Regarding Efficacy

Study B305 supports the claim that SDZ ASM 981 1% cream is superior to vehicle in the treatment of atopic dermatitis in children ages 2-17 years [(p=0.002) in the Investigator's Global Assessment at day 43 (efficacy endpoint)]. This treatment effect was seen as early as day 8 and was maintained throughout the study. Even though the efficacy endpoint chosen was day 43 (6 weeks), it is important that this drug product reached statistical significance over vehicle within 3 weeks, as this may be the longest duration that a patient may be willing to use the drug product without significant relief. The analysis on the per protocol population supported the findings in the ITT population (see statistical review). The analysis of the secondary efficacy variables, which are individual components of atopic dermatitis (erythema, papulation/induration, excoriation, lichenification, pruritus), the support the findings of the Investigator's Global Assessment.

11.3.1.5 Safety outcomes

Reviewer's Comment: The safety population consisted of the ITT population, all patients randomized and dispensed study medication. This was a total of 198 patients, 130 subjects in the ASM 1% cream arm and 68 subjects in the vehicle arm. The review of the safety data will include safety analysis of the double-blind phase (ASM 981 cream 1% and vehicle), and the open-label phase. The review of the safety data from this study will be reviewed in combination with study B307, which followed the identical protocol (see section 11.4.2).

11.4 Sponsor's protocol # CASM 981 B307

Title: "A 26-week study with a 6-week, randomized, multicenter, double-blind vehicle-controlled, parallel-group phase followed by a 20-week, open-label phase to study the safety and efficacy of 1% SDZ ASM 981 cream in pediatric subjects with atopic dermatitis"

11.4.1 Financial Disclaimer: As per Form 3454, the sponsor has certified that no financial arrangements with investigators have been made where the outcome affects compensation, and that investigators have no proprietary, significant equity, interest, or any significant payments in this clinical study performed in support of this NDA.

The results from — center. — are not out of line with the results from other centers in the study and therefore, does not unduly influence the results of the study.

11.4.2 Investigators

- | | | |
|----|----------------------|-------------------------|
| 1. | Alfred T. Lane, M.D. | 501/Stanford, CA 94305 |
| 2. | M. Irving Katz, M.D. | 502/Fridley, MN 55432 |
| 3. | Neil Korman, M.D. | 503/Cleveland, OH 44106 |
| 4. | Amy Pallor, M.D. | 504/Chicago, IL 60614 |