[pneumonia (3.9% vs. 0)], eye infection (2.5% vs. 0), pharyngitis 5 (2.5% vs. 0), respiratory tract infection NOS (2.5% vs. 0), toothache (2.9% vs. 0), rhinorrhea (3.9% vs. 0), wheezing (3.9% vs. 0), hypersensitivity (8.3% vs. 2.2%),, and irritability (2.5% vs. 0).

11.6 Sponsor's protocol # CASM981 B313

Title: "A randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of SDZ ASM 981 cream 1% in the long-term management of atopic dermatitis in children"

11.6.1 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. [redacted] who did not return the financial disclosure form. As this only comprises [redacted] and thus a small amount of patients (17), it is not felt that data from these [redacted] centers can unduly influence the outcome of the study.

11.6.2 Investigators

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11.6.1.1 Objective/Rationale

The primary objective was to investigate the 6-month efficacy and safety of SDZ ASM 981 cream 1% in the long-term management of atopic dermatitis (AD) in children. Management is defined as controlling AD by treating early signs and symptoms of the disease with SDZ ASM 981 cream 1% in order to prevent exacerbation to an extent that treatment with a second-line, topical corticosteroid medication is required. Secondary objectives included to investigate the 12-month efficacy and safety of SDZ ASM 981 cream 1% in the long term management of atopic dermatitis in children; to assess the therapeutic efficacy of SDZ ASM 981 cream 1% in children, with particular focus on the first 6 weeks of treatment, using investigator and subject assessments.

Reviewer's Comment: *This 1-year study is not considered to be a pivotal trial in which the efficacy of ASM 1% cream will be determined. It will primarily be reviewed to assess the safety of use of ASM 1% cream in the long-term treatment of atopic dermatitis.*

11.6.1.2 Design

This was a double-blind, multicenter, parallel-group study in which pediatric subjects were randomized to treatment with either SDZ ASM 981 cream 1% or a corresponding vehicle cream. Randomization was in a 2:1 ratio SDZ ASM 981 cream 1% : vehicle. Subjects were treated with study medication plus a bland emollient for 7 days after randomization. For the remainder of the 12-month study, subjects were treated according to the Guardian On/Off scheme, as described in table 47.

Table 47
Guardian's treatment on/off scheme
Study B313

Signs & Symptoms	Treatment/Action
• No evidence of atopic dermatitis apart from dry skin	• Emollient
• Evidence of itching (pruritus), such as persistent scratching or rubbing, and/or Persistent redness (erythema), and/or Thickening of the skin (infiltration)	• Study drug + emollient
• Oozing/crusting or excessive scratch marks (excoriation), and Intense redness (erythema)	Primary caregiver must contact investigative center to arrange unscheduled visit as soon as possible. Investigator must ascertain whether the criteria for treatment with a second-line, topical corticosteroid are fulfilled using the Investigator's Global Assessment ,i.e. IGA of 4 (severe) or 5 (very severe).

Second-line active treatment with moderately potent topical corticosteroids (according to label) and emollients was mandated by the protocol if the atopic dermatitis worsened to the extent that the IGA of the disease was 4 (i.e. severe) or 5 (i.e. very severe). After each cycle of second-line active treatment there was a mandatory 7-day treatment with study medication to treat any residual disease which could have resulted in a faster recurrence of the atopic dermatitis if left untreated.

The double-blind treatments were only applied to affected areas. Figure 3-1 shows the treatment scheme used for the study.

The study was designed to allow a complete analysis to be performed on 6-month data to support a claim for the use of SDZ ASM 981 cream 1% in the long-term management of atopic dermatitis in pediatric subjects.

11.6.1.3 Protocol

Key Inclusion and Exclusion Criteria:

Subjects included in the study were those:

Who were outpatients, of any gender and race, aged 2 to <18 years.

With a diagnosis of atopic dermatitis fulfilling the diagnostic criteria of Williams [3], atopic dermatitis affecting at least 5% total body surface area (estimated using area of subject's palm as approximately 1% TBSA), with an Investigator's Global Assessment score of 2 and using a stable dose of a permitted bland emollient for 1 week at baseline. (Protocol Amendment #4 (15-Nov-99) allowed subjects younger than 2 years to enter the study but this was too late to have any impact on recruitment in this age group).

Whose legal guardian had given written informed consent.

Subjects were excluded if they:

had received therapy known or suspected to affect atopic dermatitis: phototherapy or systemic therapy (including systemic corticosteroids) within 1 month prior to first application of study medication; topical therapy known to have an effect on AD (e.g., tar, topical corticosteroids) with 7 days prior to first application of study medication; systemic antibiotics within 2 weeks prior to first application of study medication.

were immunocompromised or had a history of malignant disease, or had concurrent skin disease (e.g. acne, impetigo, chicken pox, active herpes simplex at baseline, corticosteroid induced perioral dermatitis, tinea corporis/intertriginosa, head lice or scabies) that could have interfered with the evaluation.

who were known to be HIV-positive. Testing for HIV was not required.

were hypersensitive to any ingredient of the SDZ ASM 981 cream 1%, the second-line corticosteroid medication or corticosteroids in general.

were pregnant, or lactating, or were females of childbearing potential not using medically-approved contraception.

were known to be non-compliant or unreliable with respect to medical treatment or appointments, with drug abuse or mental dysfunction limiting their ability to cooperate with the study procedures, or had any other condition that the investigator felt rendered them ineligible for the study.

Second-line topical corticosteroid therapy for atopic dermatitis was to be used if the disease signs worsened despite treatment with study medication and emollients, as described in the Guardian's treatment on/off scheme (table 40). Prior to application of second-line treatment, the subject had to be examined by the investigator to ensure that the criteria for second-line treatment initiation had been met (i.e. an IGA of 4 or 5). If the subject met these criteria, a moderately potent topical corticosteroid was dispensed for use until complete clearance of the atopic dermatitis had occurred, or the maximum treatment period permitted by the product label had elapsed. All affected areas could be treated with the topical corticosteroid. Furthermore, the dispensed second-line medication was to be returned to the investigative center as soon as possible after cessation of the particular flare event. It was permitted to receive multiple cycles of second-line treatment during the study, but at least 7 days had to elapse between courses of second-line treatment. As noted previously, each course of second-line therapy was to be followed by 7 days' treatment of residual disease with study medication.

Table 48 shows the potency of the selected second line medications used in the study.

Table 48
Potency of selected second-line medication
Study B313

Second-line Medication	ATC Classification	Alternative Classification
0.02% difluprednate cream	Potent (group III)	Moderately potent[1]
0.25% prednicarbate cream	Potent (group III)	Moderately potent[2]
0.1% hydrocortisone butyrate cream	Moderately potent (group II)	Medium potency[3]
0.05% clobetasone butyrate cream	Moderately potent (group II)	Medium potency[3]
0.02% triamcinolone acetonide cream	Moderately potent (group II)	
0.2% hydrocortisone valerate cream	Weak (group I)	Medium potency[3]

[1]Saurat [4]
[2]Deutsches Aerzteblatt [5]
[3]USP DI [6]

Each participating country had a specific second-line medication selected for use. (See Protocol post-text supplement 6, and Protocol Amendments 1 and 2 (Appendix 1.1)). The criteria for selection of second-line medication were:

1. Must be a corticosteroid cream of moderate potency.
2. May be used in pediatric patients.
3. May be used on all body areas.
4. Maximum duration of use must be sufficient to allow treatment of AD flare episodes.

The maximum duration of use allowed in most participating countries was 2-4 weeks. In those countries in which no maximum duration of use was specified in the local label the investigator's clinical judgment was used.

The visit schedule and schedule of procedures is shown in table 49.

Table 49
Visit schedule and schedule of procedures
Study B313

	Scr.	Treatment Phase												SC
Visit Week		1	2	4	7	11*	15	21*	27	33*	39	45*	USV	53
Visit Day	-14 to -2	1	8	22	43	71	99	141	183	225	267	309		366
Medical history	X													
Incl./Exclusion criteria	X	B												
Informed consent	X													
QoL evaluation		B			X				X					X
Vital signs	X				X				X					X
Height/length and weight	X	X	X	X	X		X		X		X		X	X
Full physical examination	X				X				X					X
IGA	X	B	X	X	X		X		X		X		X	X
EASI evaluation		B	X	X	X		X		X		X		X	X
Other signs & symptoms of AD		B	X	X	X		X		X		X		X	X
Pruritus severity assessment		B	X	X	X		X		X		X		X	X
Subject's assessment		B	X	X	X		X		X		X		X	X
Adverse events[1]			X	X	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X	X
Drug accountability[1]			X	X	X		X		X		X		X	X
Concomitant medication[1]	X	B	X	X	X	X[d]	X	X[d]	X	X[d]	X	X[d]	X	X
Labs[2]	X								X					X
Medication applied[3]		< ---------- BID, as required ---------- >												
End of study evaluation														X
4-week follow-up for SAE's														start

Scr = Screening Phase; *Telephone monitoring of subject by investigative center; SC = Study Completion; USV =Unscheduled visit; IGA = Investigators Global Assessment; X[d] = Discussion between subject/primary care giver and investigator; B = Before first application of study medication; [1]Subject/primary care giver interview; [2]Hematology, clinical chemistry and urinalysis plus pregnancy screen for all female subjects; [3]Study Medication (applied twice daily) as required by status of disease

Reviewer's Comment: *The Investigator's Global Assessment Scale is the same as for the pivotal trials. Safety assessments were the same as in the pivotal trials but also included skin anergy testing of a subset of patients at the end of the 12-month study. Patients were also followed for 4 weeks after the end of the study or after discontinuation to monitor for any serious adverse events and to monitor events that led to discontinuation.*

11.6.1.3.1 Population

The population included patients with atopic dermatitis of at least a grade severity of 2 (on the Investigator's Global Assessment Scale) with at least 5% of total body surface area affected and who were 2 years old to less than 18 years of age. It was planned that 660 pediatric subjects (with a ratio of 2:1 for ASM to vehicle) would be recruited, anticipating that this would provide safety and efficacy data from at least 200 subjects treated for 6 months with ASM as well as obtaining safety data for at least 100 subjects treated with ASM for 12 months.

Reviewer's Comment: *The protocol is attempting to demonstrate that the use of ASM Cream 1% in the treatment of mild to moderate atopic dermatitis will reduce the number of flares of atopic dermatitis as compared to the "standard of care" (use of a topical corticosteroid). A major flaw is the study design is the mandatory use of ASM 1% cream or vehicle for seven days after treating a flare with a topical corticosteroid. Thus, patients in the ASM 1% cream arm received up to 7 more days of treatment with an active drug product as compared to the vehicle arm. The design of this study cannot support a direct comparison with a topical corticosteroid in its ability to reduce the incidence of atopic dermatitis flares.*

11.6.1.3.2 Endpoints

The primary efficacy endpoint was the ranked flares of atopic dermatitis at month 6. A flare of AD was defined in cases where, at a scheduled or unscheduled visit, the IGA was 4 or 5, and where second-line therapy was commenced within a 3-day window of such a visit and was preceded by at least 7 days off second-line therapy.

The secondary endpoint involved this same analysis at month 12. The safety endpoints included all adverse events, comparing ASM 1% cream arm with vehicle, laboratory results, and to look at an aspect of the immune system, specifically the ability to demonstrate a normal cell-mediated, delayed type hypersensitivity reaction against a range of antigens after using ASM 1% cream over the course of 1 year.

Skin anergy testing was administered to a small subset of patients in study B313 at the end of the 12 month study. The following criteria were used to select patients for skin anergy testing:

Informed consent specific for this procedure must have been received

Patient completed the study (i.e., did not discontinue early)

The patient must be three years of age or older at time of testing

Patient has received at least 2 vaccinations against diphtheria and tetanus, the last of which took place at least 8 weeks prior to testing

Patient has not received treatment with any systemic, potentially immunosuppressive medication (including oral corticosteroids, chemotherapeutic agents, antilymphocyte globulin, irradiation) in the week prior to the test.

Patient should not be suffering from diabetes mellitus, uremia, or an acquired immune deficiency disorder.

Patient should not have received live virus vaccinations (e.g., measles, mumps, rubella, poliomyelitis) for 6 weeks prior to the test.

11.6.1.3.3 Statistical considerations

The procedure adopted for calculating ranked flares, the primary efficacy variable, was based on the method proposed by Gould[8].

The primary efficacy analysis was conducted as follows. Firstly, subjects who did not discontinue from the study in the first six months were ranked according to the number of flares they experienced (zero flares being the 'best case'). Subjects who discontinued prematurely were

ranked according to the number of flares they experienced per unit time they remained on the study. Subjects that discontinued were ranked higher than those who completed the six-month phase of the study.

The primary objective of the efficacy evaluation is to compare the response in long-term management of atopic dermatitis over 26 weeks with ASM 1% and vehicle. This was addressed by investigating whether there was a statistical association between treatment and outcome. The association was assessed using a Wilcoxon rank sum test with adjustment for centers as strata (also known as the Van Elteren test). The two-sided significance level for testing treatment differences was set at 5%.

A frequency table of individual flare counts is also presented over time.

The primary efficacy analysis was also performed with data from center 13 excluded to ensure robustness of any conclusions drawn following an audit report that brought the integrity of the data supplied by this center into question.

11.6.1.4 Results

11.6.1.4.1 Populations enrolled/analyzed

There were 713 subjects randomized, 476 were randomized to ASM and 237 to vehicle cream. Of the 713 subjects randomized, 711 were dispensed study medication and hence include the ITT and safety populations (474 ASM, 236, vehicle). Table 50 shows the subject disposition for each group. A greater proportion of subjects in the ASM treatment group remained on study than did so in the vehicle group. The most common reason for discontinuation was unsatisfactory therapeutic effect; this was much more common in the vehicle group. The time to discontinuation was significantly less in the vehicle cream group, and discontinuation was more likely to occur early in both groups if the baseline disease severity was high. There was no significant difference in time to discontinuation due to adverse events.

Table 50
Subject Disposition for Each Treatment Group

Number of subjects	ASM 1% n(%)	Vehicle n(%)
Randomized	476	237
Treated	474	237
Completed 6 months	358 (75.5)	123 (51.9)
Completed 12 months	324 (68.4)	115 (48.5)
Discontinued		
All	150 (31.6)	122 (51.5)
Adverse event(s)	15 (3.2)	8 (3.4)
Abnormal lab. Values	2 (0.4)	0 (0)
Unsat. Therap. Effect	59 (12.4)	72 (30.4)
Protocol violation	21 (4.4)	15 (6.3)
Lost to follow up	15 (3.2)	7 (3.0)
Withdrawal of consent	15 (3.2)	10 (4.2)
Administrative reasons	23 (4.9)	10 (4.2)

Source: Post text table 7.1-3, 7.1-13

The number of protocol violations in the study was high, 53.6% for ASM 1% cream and 58.6% for vehicle. The largest percentage were those that used a banned medication (24.8%) and those that did not use study medication for at least 6 days in the 7 day period following second line medication (see table 51).

Table 51
Protocol Violations (Randomized Population)

Violation	ASM 1% n(%) (N=476)	Vehicle n(%) (N=237)
Number of subjects with at least one violation	256 (53.8)	139 (58.6)
Subject did not take at least 6 drug days of study medication in the first 7 days of the study	32 (6.7)	20 (8.4)
Subjects took drug o.d for more than 15% of study days	47 (9.9)	15 (6.3)
%TBSA involvement of AD of less than 5% at pre-treatment	17 (3.6)	9 (3.8)
Baseline IGA <2	1 (0.2)	0
Subject became pregnant during the study	1 (0.2)	0
Subject discontinued due to protocol violation	22 (4.6)	15 (6.3)
Subject discontinued due to lost to follow up	16 (3.4)	7 (3.0)
Subject took study medication more than b.i.d. on more than 7 days	2 (0.4)	0
No study medication records whilst on study/not treated	4 (0.8)	3 (1.3)
Subject did not take study medication for at least 6 drug days in the 7 days following second line medication	93 (19.5)	88 (37.1)
Subject took banned medication	118 (24.8)	44 (18.6)

Source: Post text table 7.2-1

Reviewer's Comment: The protocol violations are high, especially for a couple of major protocol requirements. There were 43.4% of patients who took a banned study medication (24.8% in the ASM 1% cream arm and 18.6% in the vehicle arm). The sponsor does not elaborate as to which specific medications were involved in this protocol violation. The other major protocol violation that occurred at a high percentage was subjects not using study medication at least 6 drug days after second line therapy (19.5% for the ASM 1% cream arm and 37.1% for the vehicle arm). It is suspected that many patients did not comply with this protocol requirement for many would forget to treat clinically normal skin.

Table 52 outlines the baseline demographics for the ITT population. Most of the subjects were Caucasian. The two treatment groups were well balanced with respect to demographic characteristics, with no significant between-group differences in age, sex, race, height or weight. The study did recruit a significant number of patients under the age of 8, with 29.3% (208/711) of the study population was aged 4 years or under.

Table 52
Baseline demographics (ITT population)

Treatment group	ASM 1% (N=474)	Vehicle (N=237)
Age (years)		
mean ± SD	8.0 ± 4.56	7.9 ± 4.55
median	7.0	7.0
range	1-17	2-17
Distribution (n %)		
<2 years	3 (0.6)	0 (-)
2<12 years	348 (73.4)	178 (75.1)
12<18 years	123 (25.9)	59 (24.9)
Sex (n, %)		
Male	224 (47.3)	112 (47.3)
Female	250 (52.7)	125 (52.7)
Race (n, %)		
Caucasian	376 (79.3)	195 (82.3)
Black	19 (4.0)	7 (3.0)
Oriental	26 (5.5)	14 (5.9)
Other	53 (11.2)	21 (8.9)
Weight (kg)		
mean ± SD	31.9 ± 18.95	31.5 ± 16.67
range	8.1-111.5	11.5- 92.0
Height (cm)		
mean ± SD	128.4 ± 26.49	128.1 ± 25.90
range	79.0-186.0	84.0-178.5

Source: Post-text table 7.4-1

Baseline AD characteristics were similar between the two treatment groups. The mean body surface area affected was approximately 25% in both groups, with a majority of subjects in both groups having an IGA score of 3 (moderate disease).

Drug exposure was measured by treatment days and drug days. Treatment days refer to the number of days the subject received study medication (ASM 1% cream or vehicle). Drug days take subject compliance into account: one drug day is assigned if study medication was applied b.i.d. or more), 0.5 days if o.d., and 0 days if study medication was not applied on a given day. The overall exposure by median treatment and drug days for ASM cream 1% was 205 and 192.5 days, respectively for the twelve-month study. For the vehicle overall exposure by median treatment and drug days was 111 and 106 days, respectively. The lower mean treatment and drug days in the vehicle group was probably due to a higher discontinuation rate and their greater use of topical corticosteroids.

11.6.1.4.2 Efficacy endpoint outcomes

A primary objective of this study, was to assess the long-term management of atopic dermatitis by comparing flares of atopic dermatitis between ASM 1% cream and vehicle. Tables 53 and 54 show the incidence of flares at 6 months and 12 months, respectively.

Table 53
Incidence of flares of AD (ITT population)

Treatment group	ASM 1% (N=474) n(%)	Vehicle (N=237) n(%)
Completed 6 months	358 (75.5)	123 (51.9)
0 flares	289 (61.0)	81 (34.2)
1 flare	48 (10.1)	24 (10.1)
2 flares	12 (2.5)	12 (5.1)
>2 flares	9 (1.9)	6 (2.5)
Discontinued prior to month 6	116 (24.5)	114 (48.1)
0 flares	69 (14.6)	34 (14.3)
1 flare	35 (7.4)	48 (20.3)
2 flares	9 (1.9)	26 (11.0)
>2 flares	3 (0.6)	6 (2.5)
p-value[1]	<0.001	

[1] Between-group comparison p<0.001, Van Elteren test, stratified by center, on ranked flares

A flare occurs in cases where, at a scheduled or unscheduled visit, the IGA was assessed to be either a score of 4 or 5, where second-line therapy is commenced within a 3-day window of this visit and is preceded by at least 7 days off second-line therapy. The incidence of flares are then ranked, with subjects discontinuing considered worse than those subjects that stay on study.

Subjects discontinuing are ranked according to the number of flares they experience over unit time on study; subjects completing the study are ranked according to the number of flares recorded.

Source: Post-text table 9.1-1

Table 54
Incidence of flares of AD (ITT population)

Treatment group	ASM 1% (N=474) n(%)	Vehicle (N=237) n(%)
Completed study (12 months)	324 (68.4)	115 (48.5)
0 flares	241 (50.8)	67 (28.3)
1 flare	56 (11.8)	27 (11.4)
2 flares	14 (3.0)	12 (5.1)
>2 flares	13 (2.8)	9 (3.8)
Discontinued (total)	150 (31.6)	122 (51.5)
0 flares	83 (17.5)	36 (15.2)
1 flare	46 (9.7)	52 (21.9)
2 flares	15 (3.2)	28 (11.8)
>2 flares	6 (1.2)	6 (2.5)
p-value[1]	<0.001	

[1] Between-group comparison p<0.001, Van Elteren test, stratified by center, on ranked flares

A flare occurs in cases where, at a scheduled or unscheduled visit, the IGA was assessed to be either a score of 4 or 5, where second-line therapy is commenced within a 3-day window of this visit and is preceded by at least 7 days off second-line therapy. The incidence of flares are then ranked, with subjects discontinuing considered worse than those subjects that stay on study.

Subjects discontinuing are ranked according to the number of flares they experience over unit time on study; subjects completing the study are ranked according to the number of flares recorded.

Source: Post-text table 9.2-1

Tables 55 and 56 show the percentage of subjects using second-line therapy and days on second-line therapy, respectively.

Table 55
Second-line Topical Corticosteroid Therapy (ITT population)
Study B313

Second-line medication	ASM 1% (N=474) n (%)	Vehicle (N=237) n (%)
Any second-line therapy	163 (34.4)	148 (62.4)
0.02% difluprednate cream	15(3.2)	10 (4.2)
0.25% prednicarbate cream	31 (6.5)	32 (13.5)
0.1% hydrocortisone butyrate cream	26 (5.5)	40(16.9)
0.05% clobetasone butyrate cream	69 (14.6)	52 (21.9)
0.02% triamcinolone acetonide cream	3(0.6)	0 (0)
0.2% hydrocortisone valerate cream	18(3.8)	15(6.3)

Source: Post-text table 8.2-3

Table 56
Days on Second Line Therapy (ITT population) (12 month data)

Study B313

Baseline IGA		N	Days on second-line therapy, N (%)				
			0	1-7	8-14	15-21	22+
Overall	ASM 1%	474	311 (65.6)	39 (8.2)	34 (7.2)	27 (5.7)	63 (13.3)
	Vehicle	237	89 (37.6)	37 (15.2)	30 (12.7)	24 (10.1)	57 (24.1)
Mild	ASM 1%	122	99 (81.1)	7 (5.7)	3 (2.5)	5 (4.1)	8 (6.6)
	Vehicle	64	36 (56.3)	9 (14.1)	6 (9.4)	4 (6.3)	9 (14.1)
Moderate	ASM 1%	262	177 (67.6)	23 (8.8)	17 (6.5)	13 (5.0)	32 (12.2)
	Vehicle	120	41 (34.2)	17 (14.2)	17 (14.2)	13 (10.8)	32 (26.7)
Severe	ASM 1%	74	27 (36.5)	7 (9.5)	14 (18.9)	7 (9.5)	19 (25.7)
	Vehicle	42	10 (23.8)	8 (19.0)	6 (14.3)	6 (14.3)	12 (28.6)

Source: Post-text table 8.2-6, 8.2-8

Reviewer's Comment: *The results of this trial are supportive of the pivotal efficacy trials in that the number of subjects who do not experience any flares on ASM 1% cream when compared to vehicle at the 6-month time point is almost double that of those treated with vehicle (61.0% and 34.2%, respectively, see table 45). This is maintained at the 12-month time point with those not experiencing flares on ASM cream 1% comprising 50.8% of the population compared to 28.3% of those subjects on vehicle. There is not a large difference in the number of flares experienced between the two arms at the 6-month time point. Both ASM 1% cream and vehicle arms had 10.1% of patients who experienced one flare. The difference in flares for ASM 1% cream and vehicle for 2 flares was 2.5% and 5.1%, respectively and for >2 flares it was 1.9% and 2.5%, respectively. This difference might be attributed to the fact that subjects in the ASM 1% cream arm, after a flare in which a topical corticosteroid was used, those patients were then treated with ASM 1% cream for 7 days. Thus, patients in the ASM 1% cream arm received more "medical" treatment than did those in the vehicle arm.*

11.6.1.4.3 Conclusions Regarding Efficacy Data

This study, B313, a one-year study of pediatric patients ages 2 – 17 years old, is supportive of the efficacy data in the pivotal trials. However, it does not provide any regulatory utility for the claim of reducing the number of flares in atopic dermatitis as compared to the "standard of care", in particular reduction of use of topical corticosteroids. The main usefulness of this trial is its safety profile.

11.6.1.4.5 Safety outcomes

The safety population comprised 711 patients ages 2 – 17 years old, 474 on ASM 1% cream and 237 on vehicle. Again, patients in both arms were allowed to be treated with a topical corticosteroid if they experienced a flare of atopic dermatitis (IGA severity score of 4 or 5). The mean number of treatment days for subjects on ASM 1% cream was 205 (7.3 months) and for vehicle the mean number of treatment days for subjects was 111 days (4 months). What follows is this reviewer's analysis of the safety issues addressed by study B313.

There are three main safety questions that this 1 year long-term study may determine in pediatric patients ages 2-17. First, is there an increase in the adverse event profile attributable to ASM 1% cream alone in the long term study (duration of 1 year) as compared to the short-term studies (duration of 20-26 weeks)? Second, is there an increase in incidence of adverse events when sequential use of a topical steroid cream is employed with ASM 1% cream? Third, is there an effect on the immune system after use of ASM 1% cream over a period of 1 year as determined by skin anergy testing?

To answer the first question, only patients in the ASM 1% cream arm that did not use topical corticosteroids during the year of the trial were compared to those in the open-label trials who were allowed to use ASM 1% cream up to 26 weeks. Table 57 shows the comparison of these two arms of the trials.

Table 57
Incidence of Common Adverse Events (≥1%) in Patients On ASM 1% Cream
Comparison of 26 weeks (Studies B305 & B307) to 52 weeks (Study B313)
Safety Population

	ASM 1% (26 weeks) (N=335)[a] N (%)	ASM 1% (1 year) (N=272)[b] Not using CS[1]	P-value[a]
At least 1 AE	240(72.0%)	230(84.6%)	0.001
Infections and infestations			
Upper Respiratory Tract Infection NOS	65 (19.4%)	13 (4.8%)	0.001
Nasopharyngitis	32 (19.6%)	72 (26.5%)	0.001
Skin Infection	18 (5.4%)	6 (2.2%)	0.041
Influenza	22 (6.6%)	36(13.2%)	0.006
Ear Infection NOS	19 (5.7%)	9 (3.3%)	NS
Otitis Media	10 (3.0%)	8 (2.9%)	NS
Impetigo NOS	12 (3.6%)	11 (4.0%)	NS
Bacterial Infection	4 (1.2%)	3 (1.1%)	NS
Sinusitis	11 (3.3%)	6 (2.2%)	NS
Pneumonia NOS	5 (1.5%)	0	
Pharyngitis Streptococcal	10 (3.0%)	0	
Molluscum Contagiosum	4 (1.2%)	5 (1.8%)	0.524
Staphylococcal Infection NOS	7 (2.1%)	0	
Herpes Simplex	4 (1.2%)	9 (3.3%)	0.073
Bronchitis NOS	3 (0.9%)	29 (10.7%)	0.001
Tonsillitis	3 (0.9%)	17 (6.3%)	0.001
Viral Infection NOS	1 (0.3%)	18 (6.6%)	0.001
Gastroenteritis NOS	2 (0.6%)	20 (7.4%)	0.001
Chickenpox	3 (0.9%)	8 (2.9%)	0.058
Folliculitis	3 (0.9%)	6 (2.2%)	0.311
Skin Papilloma	2 (0.6%)	9 (3.3%)	0.015
Tonsillitis Acute NOS	3 (0.9%)	7 (2.6%)	0.105
Superinfection	0	2 (0.7%)	NS
Upper Respiratory Tract Infection Viral NOS	3 (0.9%)	4 (1.5%)	NS
Herpes Simplex Dermatitis	1 (0.3%)	4 (1.5%)	0.105
Bronchitis Acute NOS	0	4 (1.5%)	0.040
Eye Infection NOS	0	3 (1.1%)	0.287
Pharyngitis NOS	3 (0.9%)	22 (8.1%)	0.001
General disorders and administration site conditions			
Application Site Burning	5 (1.5%)	23 (8.5%)	0.001
Pyrexia	41 (12.2%)	34 (12.5%)	NS

	ASM 1% (26 weeks) (N=335)[a] N (%)	ASM 1% (1 year) (N=272)[b] Not using CS[1]	P-value*
Application Site Reaction NOS	7 (2.1%)	9 (3.3%)	NS
Application Site Irritation	2 (0.6%)	5 (1.1%)	NS
Application Site Pruritus	2 (0.6%)	1 (0.4%)	NS
Influenza Like Illness	2 (0.6%)	5 (1.8%)	NS
Application Site Erythema	0	6 (2.2%)	0.008
Respiratory, thoracic and mediastinal disorders			
Cough	31 (9.3%)	43 (15.8%)	0.014
Nasal Congestion	6 (1.8%)	4 (1.5%)	NS
Rhinorrhea	3 (0.9%)	1(0.4%)	NS
Asthma Aggravated	13 (3.9%)	3 (1.1%)	0.026
Asthma NOS	11 (3.3%)	10 (3.7%)	NS
Rhinitis	5 (1.5%)	12 (4.4%)	0.029
Wheezing	4 (1.2%)	2 (0.7%)	NS
Dyspnea NOS	0	5 (1.8%)	0.018
Epistaxis	0	9 (3.3%)	0.006
Gastrointestinal disorders			
Abdominal Pain Upper	10 (3.0%)	15 (5.5%)	0.120
Sore Throat	15 (5.4%)	22 (8.1%)	0.065
Vomiting NOS	14 (4.2%)	18 (6.6%)	0.183
Diarrhea NOS	2 (0.6%)	18 (6.6%)	0.001
Nausea	4 (1.2%)	11 (4.0%)	0.023
Abdominal Pain NOS	5 (1.5%)	12 (4.4%)	0.029
Looses Stools	4 (1.2%)		
Toothache	1 (0.3%)	7 (2.6%)	0.025
Constipation	2 (0.6%)	10 (3.7%)	0.005
Musculoskeletal, Connective Tissue and Bone Disorders			
Arthralgias	1 (0.3%)	3 (1.1%)	
Reproductive System and Breast Disorders			
Dysmenorrhea	5 (1.5%)	3 (1.1%)	NS
Eye Disorders			
Conjunctivitis NEC	7 (2.1%)	6 (2.2%)	NS
Skin & Subcutaneous Tissue Disorders			
Urticaria	1 (0.3%)	1 (1.5%)	NS
Acne NOS	1 (0.3%)	4 (1.5%)	NS
Blood and Lymphatic System Disorders			
Lymphadenopathy	2 (0.6%)	2 (0.7%)	NS
Immune System Disorders			
Hypersensitivity NOS	16 (4.8%)	14 (5.1%)	NS
Ear and Labyrinth Disorders			
Earache	0	8 (2.7%)	0.002
Nervous system disorders			
Headache	38 (11.3%)	69 (25.4%)	0.001

Source: Adapted from post-text tables 10.1-13 and 10.1-28 Volumes 1-157 and 1-172; post text table 1.2-4; Vol. BZ

[a] combined subjects from open-label phase of studies B305 and B307

[b] subjects on ASM 1% cream in study B313 who did not use topical corticosteroids at any time in the study

[1] topical corticosteroid

*Chi Square Test or Fisher's Exact Test if 25% of the cells have expected counts less than 5.

Table 57 shows that for two adverse events, clinical significance that was found at 26 weeks over use at 6 weeks was maintained after 52 weeks. These events were nasopharyngitis

(19.6% at 26 weeks, 26.5% at 52 weeks) and influenza (6.6% at 26 weeks, 13.2% at 52 weeks). There are, however, several new treatment emergent adverse events that become statistically significant when used over a 52-week period versus use over a 26-week period. These include headache (11.3% vs. 25.4%), bronchitis NOS (0.9% vs. 10.7%), tonsillitis (0.9% vs. 6.3%), viral infection NOS (0.6% vs. 6.6%), gastroenteritis NOS (0.6% vs. 7.4%), skin papilloma (0.6% vs. 3.3%), bronchitis acute NOS (0 vs.1.5%), pharyngitis NOS (0.9%, vs. 8.1%), cough (9.3% vs. 15.8%), rhinitis (1.5% vs. 4.4%), dyspnea NOS (0 vs. 1.8%), epistaxis (0 vs. 3.3%), diarrhea (0.6%, vs. 6.6%), nausea (1.2% vs. 4.0%), toothache (0.3% vs. 2.6%), constipation (0.6% vs. 3.7%), earache (0 vs. 2.7%),and application site erythema (0 vs. 2.2%). The data suggests that the longer one uses the drug, there is an increase risk of infection, particularly viral infections.

The sponsor had a concern that over time, irrespective of continued drug use, the incidence of infections would normally rise and therefore, the incidence of adverse events after being on ASM 1% cream arm for 1 year would not be attributable to the drug product itself. In an attempt to look at this parameter, a comparison was made between subjects on ASM 1% cream and who were on vehicle for 1 year (without prn topical corticosteroids, per protocol). The results are shown in table 58.

Table 58
Incidence of Common Adverse Events (≥1%)
ASM 1% Cream and Vehicle for One Year
Safety Population – Study B313

	ASM 1% (1 year) (N=272) Not using CS[1]	Vehicle (1 year) (N=75) Not using CS[1]
At least 1 AE	230(84.6%)	56(74.7%)
Infections and infestations		
Upper Respiratory Tract Infection NOS	13 (4.8%)	6 (8.0%)
Nasopharyngitis	72 (26.5%)	16 (21.3%)
Skin Infection	6 (2.2%)	3 (4.0%)
Influenza	36(13.2%)	3 (4.0%)
Ear Infection NOS	9 (3.3%)	1 (1.3%)
Otitis Media	8 (2.9%)	4 (5.3%)
Impetigo NOS	11 (4.0%)	4 (5.3%)
Bacterial Infection	3 (1.1%)	0
Sinusitis	6 (2.2%)	1 (1.3%)
Pneumonia NOS	0	1 (1.3%)
Pharyngitis Streptococcal	0	<1%*
Molluscum Contagiosum	5 (1.8%)	0
Staphylococcal Infection NOS	0	<1%*
Herpes Simplex	9 (3.3%)	2 (2.7%)
Bronchitis NOS	29 (10.7%)	6 (8.0%)
Tonsillitis	17 (6.3%)	0
Viral Infection NOS	18 (6.6%)	1 (1.3%)
Gastroenteritis NOS	20 (7.4%)	2 (2.7%)
Chickenpox	8 (2.9%)	3 (4.0%)
Folliculitis	6 (2.2%)	3 (4.0%)
Skin Papilloma	9 (3.3%)	<1%*
Tonsillitis Acute NOS	7 (2.6%)	0
Superinfection	2 (0 7%)	<1%*
Upper Respiratory Tract Infection Viral NOS	4 (1.5%)	0
Herpes Simplex Dermatitis	4 (1.5%)	<1%*

	ASM 1% (1 year) (N=272) Not using CS[1]	Vehicle (1 year) (N=75) Not using CS[1]
Bronchitis Acute NOS	4 (1.5%)	0
Eye Infection NOS	3.1 (1.1%)	<1%#
Pharyngitis NOS	22 (8.1%)	2 (2.7%)
General disorders and administration site conditions		
Application Site Burning	23 (8.5%)	5 (6.7%)
Pyrexia	34 (12.5%)	4 (5.3%)
Application Site Reaction NOS	9 (3.3%)	2 (2.7%)
Application Site Irritation	5 (1.1%)	3 (4.0%)
Influenza Like Illness	5 (1.8%)	2 (2.7%)
Application Site Erythema	6 (2.2%)	0
Respiratory, thoracic and mediastinal disorders		
Cough	43 (15.8%)	8 (10.7%)
Nasal Congestion	4 (1.5%)	1 (1.3%)
Rhinorrhea	1(0.4%)	1 (1.3%)
Asthma Aggrevated	3 (1.1%)	1 (1.3%)
Asthma NOS	10 (3.7%)	2 (2.7%)
Rhinitis	12 (4.4%)	5 (6.7%)
Epistaxis	9 (3.3%)	1 (1.3%)
Dyspnea NOS	5 (1.8%)	1 (1.3%)
Gastrointestinal disorders		
Abdominal Pain Upper	15 (5.5%)	5 (6.7%)
Sore Throat	22 (8.1%)	4 (5.3%)
Vomiting NOS	18 (6.6%)	6 (8.0%)
Diarrhea NOS	18 (6.6%)	4 (5.3%)
Nausea	11 (4.0%)	5 (6.7%)
Abdominal Pain NOS	12 (4.4%)	3 (4.0%)
Toothache	7 (2.6%)	1 (1.3%)
Constipation	10 (3.7%)	<1%#
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgias	3 (1.1%)	1(1.3%)
Reproductive System and Breast Disorders		
Dysmenorrhea	3 (1.1%)	1 (1.3%)
Eye Disorders		
Conjunctivitis NEC	6 (2.2%)	3 (4.0%)
Skin & Subcutaneous Tissue Disorders		
Urticaria	1 (1.5%)	<1%#
Acne NOS	4 (1.5%)	<1%#
Blood and Lymphatic System Disorders		
Lymphadenopathy	2 (0.7%)	1 (1.3%)
Immune System Disorders		
Hypersensitivity NOS	14 (5.1%)	1 (1.3%)
Ear and Labyrinth Disorders		
Earache	8 (2.7%)	2 (2.7%)
Nervous system disorders		
Headache	69 (25.4%)	12 (16.0%)

Source: Post-test tables 1.2-4 and 1.2-5 Volume BZ submitted 10/12/01

[1]Corticosteroid .

table provided by sponsor was only for adverse events ≥ 1%, therefore may also be 0.

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Table 58 demonstrates that the trend of the incidence of adverse events is similar when comparing ASM 1% cream and vehicle over a year of use with that of comparing ASM 1% cream used over 6 months with that of 1 year. The data continues to suggest an increase in infection when ASM 1% cream is used over a year as compared to vehicle, particularly in viral infections. For some adverse events the difference is not as great as sited in table 57 (i.e. nasopharyngitis, 26.5% vs. 21.3%), for others it is maintained (i.e. skin papilloma, 3.3% vs. <1%), but only 2 fall completely off the list for the difference is < 1% (dyspnea and earache). In table 57, some of the adverse events may loose statistical significance when compared to vehicle but all still occur at an incidence > 1% in the ASM 1% arm when compared to vehicle. Others to be added to that list from table 58 include pyrexia (8.5% vs. 6.7%), hypersensitivity NOS (5.1% vs. 1.3%), sore throat (8.1% vs. 5.3%), tonsillitis acute (2.6% vs. 0%), ear infection (3.3% vs. 1.3%), molluscum contagiosum (1.8% vs. 0%), upper respiratory tract infection viral (1.5% vs. 0%), herpes zoster (1.1% vs. 0%), and bacterial infection (1.1% vs. 0%). Administration site disorders that become apparent are application site erythema (2.2% vs. 0%) and application site burning (8.5% vs. 6.7%).

The data from this trial shows that there is an increased risk to local adverse events, primarily infectious, when topical corticosteroids are used sequentially with ASM 1% cream. The exception to this is the increased incidence of rhinitis. The statistically significant events are listed in table 59.

Table 59
Statistically Significant Adverse Events With and Without Topical Corticosteroid Use
ASM 1% Cream Arm – Study B313
N=474

	ASM 1% Using Topical CS[1] N=202 N (%)	ASM 1% Not UsingTopical CS[1] N=272 N (%)	P value*
Infections and infestations			
Impetigo	23 (11.4%)	11 (4.0%)	0.003
Skin Infection	21 (10.4%)	6 (2.2%)	<0.001
Superinfection	8 (4.0%)	2 (0.7%)	0.022
Respiratory, thoracic and mediastinal disorders			
Rhinitis	19 (9.4%)	12 (4.4%)	0.038
Skin & subcutaneous Tissue Disorders			
Uriticaria	10 (5.0%)	1 (0.4%)	0.001

Source: Post-text table 1.2-4, Volume BZ
[1]corticosteroid
* Fisher's Exact Test

The third long-term safety issue involves ascertaining if ASM 1% cream had any effect on the immune system, via skin anergy testing. One hundred and twelve patients who completed the study underwent testing, 82 patients from the ASM 1% cream arm and 30 patients from the

vehicle arm. This subset of patients had a greater mean duration of exposure during the last 5 months of the study (118.2 days) than did those patients not selected for anergy testing (96.9 days). The days from the last day of treatment until the test was applied was also shorter for those undergoing skin anergy testing (10.2 days) than those who did not receive the test (27.4 days).

The results were analyzed from two different perspectives, both comparing ASM 1% subjects to vehicle. The sponsor analyzed the subjects comparing the frequency of positive antigen responses. These results can be seen in table 60. The frequency of an absence of response to any antigen was also analyzed by this reviewer and those results are shown in table 61.

Table 60
Frequency Table of Positive Antigen Response
Safety Population (N=112)
Study B313

Antigen	ASM (N=82) n(%)	Vehicle (N=30) n(%)	p-value
Tetanus	52 (63.4%)	18 (60.0%)	0.826
Diptheria	35 (42.7%)	7 (23.3%)	0.079
Streptococcus	6 (7.3%)	0	0.190
Tuberculin	14 (17.1%)	4 (13.3%)	0.776
Candida	11 (13.4%)	1 (3.3%)	0.176
Trichophyton	7 (8.5%)	3 (10.0%)	0.726
Proteus	15 (18.3%)	2 (6.7%)	0.151
Negative Control	3 (3.7%)	0	0.563
Source Post-text table 10.4-4			

Table 61
Frequency of Absence of Antigen Response
Safety Population (N=112)
Study B313

	ASM 1 % (N=82)	Vehicle (N=30)
Absence of Antigen Response	14 (17.1%)	7 (23.3%)
Absence of Antigen Response and no topical steroid use	3 (3.7%)	3 (10.0%)

Both of these tables reveal that ASM 1% cream does not cause a complete blunting of the cellular immune response as measured by skin anergy testing is not adverse when compared to vehicle.

Laboratory evaluations were performed for each subject at baseline, at month 6, and at month 12. There were few abnormalities and no clinically significant difference between ASM subjects and vehicle subjects. The most notable abnormality was eosinophilia and basophilia. Notable eosinophilia was reported in 22.2% of ASM subjects at baseline and 22.4% subjects post-baseline. A similar pattern was observed in the vehicle group with 18.1% subjects having

notable eosinophilia at baseline and 17.3% post-baseline. Basophilia was present in 19.4% subjects at baseline and 14.6% subjects post-baseline in the ASM group and 22.7% subjects at baseline and 13.5% of subjects post-baseline in the vehicle group. It is agreed with the sponsor that this finding is not unexpected in atopic individuals.

11.7 Sponsor's protocol # CASM981 B308-E-00

Title: "A Multicenter, Parallel Group, Double-Blind, Active Controlled Study to Evaluate the Long-Term Safety and Efficacy of SDZ ASM 981 Cream Applied Twice Daily for Up to 12 Months in Subjects with Atopic Dermatitis"

11.7.1 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.

[ ]

11.7.2 Overview

This study enrolled 658 adult subjects with atopic dermatitis who had at least 5% of their body surface area involved with disease. Three hundred twenty-eight patients were randomized to the ASM 1% arm and 330 to the control arm which was triamcinolone acetonide cream, 0.1% (hydrocortisone acetate cream 1% for face, neck, and intertriginous areas). The majority of the patients had moderate (score 4.5-7.5) to severe (score 8-9) disease, with 426 patients having moderate disease and 115 patients having severe disease. The distribution between ASM and control was approximately 50%. Patients applied the medication twice daily until complete clearance of inflammation was achieved and pruritus had ceased. Treatment was repeated when symptoms recurred. The median number of treatment days for those on ASM 1% cream was 137.5 days (19.6 weeks).

There were no major between group differences in baseline demographic or disease characteristics. The rate of premature discontinuation was higher in the ASM 1% group (58.5% of subjects) than in the control group (23.9%), primarily due to lack of efficacy (36.3% versus 8.2%, respectively). This discontinuation in the ASM 1% cream arm occurred primarily within the first 4 months of the study and in patients with more severe disease.

With respect to topical steroids, in a head-to-head comparison, this trial revealed that adult patients treated with a moderately potent topical corticosteroid had a statistically significant superior response than did ASM 1% patients at all time points ($p<0.001$). See table 62.

Table 62
Proportion of Subjects with Moderately Clear or Better, According to Investigator (ITT Population, LOCF analysis)

	N/N (%) Success[1]		
	SDZ ASM 981 1%	Control	p-value
Day 8	119/322 (37.0%)	217/321 (67.6%)	<0.001
Day 22	171/326 (52.5%)	249/326 (76.4%)	<0.001
Month 6	177/327 (54.1%)	269/326 (82.5%)	<0.001
Month 12	171/327 (52.3%)	267/326 (81.9%)	<0.001
Source: post-text table 9.2-31			

[1]Defined as score of 0, 1, 2, or 3

Reviewer's Comment: *This head to head comparison suggests, that for adult patients, response of disease occurs faster with topical corticosteroids. However, as this is only one study, this conclusion is tentative, at best. This trial does demonstrate that subjects with milder disease tended to complete the one year study and not drop out, thus supporting the data in the pivotal pediatric trials that ASM cream 1% is appropriate for treatment of mild to moderate disease. Although there is not a vehicle comparator in this trial, the safety outcomes can be analyzed as in an open-label study. This analysis follows.*

11.7.3. Safety Results

Thirty-five subjects discontinued from the study due to adverse events. Twenty-five of the 35 subjects (71%) discontinued due to application site reactions, with application site burning being the most frequent reason. Over two-thirds of these events occurred over the first 28 days of the study and only 4 subjects discontinued for this reason after 2 months.

Serious adverse events that affected the skin of adult patients on ASM 1% cream were one case each of toxicoderma, contact dermatitis, infected eczema, condition aggravated and 2 cases of herpes simplex dermatitis (Kaposi's Varicelliform Eruption).

Table 63 lists the incidence of adverse events ≥ 1% that occurred during this 12 month study in adults on ASM 1% cream.

Table 63
Incidence of Most Frequent (≥1%) Treatment Emergent Adverse Events In Adults on ASM 1% Cream – Study B308*

Organ Class and Preferred Term	ASM 1% Cream (N=328) N = (%)
Total number of subjects with at least one AE	256 (78.0%)
Infections and Infestations	
Total	137 (41.8%)
Nasopharyngitis	25 (7.6%)
Influenza	32 (9.8%)
Folliculitis	20 (6.1%)
Skin infection NOS	21 (6.4%)
Herpes Simplex	13 (4.0%)
Upper respiratory tract infection NOS	14 (4.3%)
Bronchitis NOS	8 (2.4%)
Impetigo NOS	8 (2.4%)
Gastroenteritis NOS	6 (1.8%)
Furuncle (exc Genital)	4 (1.2%)
General Disorders and Administration Site Conditions	
Total	152 (46.3%)
Application site burning	85 (25.9%)
Application site reaction NOS	48 (14.6%)
Application site irritation	21 (6.4%)
Application site pruritus	18 (5.5%)
Condition aggravated	8 (2.4%)
Application site erythema	7 (2.1%)
Influenza like illness	6 (1.8%)
Pyrexia	4 (1.2%)
Nervous System Disorders	
Total	29 (8.8%)
Headache NOS	23 (7.0%)
Respiratory, Thoracic, and Mediastinal Disorders	
Total	35 (10.7%)
Asthma NOS	8 (2.4%)
Cough	8 (2.4%)
Rhinitis	7 (2.1%)
Asthma Aggravated	6 (1.8%)
Rhinitis Seasonal	6 (1.8%)
Eye Disorders	
Total	15 (4.6%)
Conjunctivitis	10 (3.0%)
Gastrointestinal Disorders	
Total	42 (12.8%)
Sore throat NOS	12 (3.7%)
Diarrhea NOS	7 (2.1%)
Nausea	6 (1.8%)
Skin and Subcutaneous Tissue Disorders	
Total	45 (13.7%)
Eczema infected	10 (3.0%)
Erythema NEC	8 (2.4%)
Acne NOS	6 (1.8%)
Sweating increased	4 (1.2%)
Musculoskeletal, Connective Tissue and Bone Disorders	
Total	17 (5.2%)
Back pain	6 (1.8%)
Arthralgia	5 (1.5%)
Immune System Disorders	
Total	12 (3.7%)
Hypersensitivity NOS	11 (3.4%)
Reproductive System and Breast Disorders	
Total	9 (2.7%)
Dysmenorrhea	4 (1.2%)
Surgical and Medical Procedures	
Total	5 (1.5%)
Post-operative pain	4 (1.2%)

*adapted from post-text table 5.1-172a, volume 9.12 and table 10-1, volume 1.208, pgs. 51-52

Reviewer's Comment: *The adverse event profile of adults indicates that adults had a greater than 2 times incidence of general disorders and administration site conditions than did the pediatric patients ages 2-17 years old (46.3% vs. 21.3% in the double blind phase of the pediatric studies). This was primarily due to application site conditions, application site burning being a case in point, where the adults experienced an incidence of 25.9% compared to the pediatric rate of 10.4%. This is probably due to adults discerning the effect and verbalizing better than children, especially those in the youngest age group (2-5 years). Adults also had a greater overall incidence of skin and subcutaneous disorders than did children, 13.7% and 5.1% respectively.*

A high incidence of infection with just under half of the patients experiencing these events, 41.8%, occurred in the adult trial. This high incidence of infection in the adult study is consistent with the incidence of infection noted in the pediatric trials of children ages 2 – 17 years old where in the open-label phase of these studies, the combined incidence rate of infection was just over half of the patients, 53.0%. Like this category, for most general categories, adults had a lower but comparable incidence of adverse events as compared to these pediatric patients. A few exceptions of note where the incidence was higher in adults include folliculitis (6.1% vs. 2.2%), skin infection NOS (6.4% vs. 2.2%), herpes simplex (4.0% vs.3.3%), eczema infected (3.0% vs. 0.7%), and erythema NEC (2.4% vs. 0%) when compared to the one-year safety data of pediatric patients ages 2-17 years.

12 Overview of Efficacy

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 patients with atopic dermatitis over a 6 week period. 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. In some of the discussion to follow, results from study 316, the infant study, because it is a unique subset with a higher skin surface ratio to body mass, may be discussed separately.

The trial design was adhered to well during the studies. There was not a statistical significant difference found among the patients regarding baseline demographics in any of the studies. The median age for studies B305 and B307 was 6.7 years. It is important to note that 47.6% of the patients in these studies was ≤5 years of age and 65.6% of the subjects in this age group were in the ASM 1% cream arm of the study. The mean weight was 29.6 kilograms and the mean height was 121.0 centimeters. There was a fair representation of ethnic groups in these two studies with 52.6% White subjects, 22.8% Black subjects, 6.7% Oriental, and 17.9% of subjects classifying themselves as "Other". There is not a specific listing for "Hispanic", however, these subjects may have included themselves in the "White" or "Other" category. The male/female ratio for both studies combined was approximately 50%. The mean total body surface area of involvement was 25.9% in studies B305 and B307. Two hundred forty-seven out of the 403 subjects (61.3%) had a %TBSA of ≥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.

The mean age for study B316, the infant study, was 12.65 months. There were 91 infants out of 186 patients (49%) that were ≤12 months of age and 65% of these infants were in the ASM 1% cream arm. The mean height was 74.9 centimeters and the mean weight was 9.7 kilograms. Although the majority of subjects in the study were White (58.6%), when taken together there was a fair representation of ethnic groups with 10.8% Black, 2.2% Oriental, and 28.5% who classified themselves as "Other". It should be noted that although the sponsor did not have a "Latin" or "Hispanic" category, there were a number of centers in both Brazil and Spain in this particular study. There were slightly more males in this study, 54.8%. 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 ≥15%, reflecting a moderate body surface area of disease activity.

The discontinuation rate in all three studies was higher in the vehicle arm, as would be expected, than in the ASM 1% cream arm, primarily due to unsatisfactory therapeutic effect. The discontinuation rate in the infant study was almost twice that of the children studies, 47.6% and 24.8%, respectively. Discontinuation in the ASM 1% cream arms for studies B305/B307 and study B316 was approximately the same, 11.3% and 11.4%. Unsatisfactory therapeutic response and lost to follow-up were the two main reasons in subjects ages 2-17 years and unsatisfactory therapeutic response was the main reason in infants.

The mean daily exposure to study medication in studies B305/307 was 39.3 days for the ASM 1% cream arm and 35.2 days for the vehicle arm. In study B316, the mean daily exposure to study medication was 37.2 days for the ASM 1% cream arm and 31.0 treatment days for the vehicle arm.

Treatment success 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). 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 (see table 64).

Table 64
Treatment Success – Investigator's Global Assessment
Double-Blind Phase – Protocols B305, B307, B316

	ASM 1%				Vehicle			
	B305 N=130	B307 N=137	B316 N=123	Pooled N=390	B305 N=68	B307 N=68	B316 N=63	Pooled N=199
Day 8	19 (14.6%)	13 (9.5%)	21 (17.1%)	53 (13.6%)	1 (1.5%)	2 (2.9%)	6 (9.5%)	9 (4.5%)
Day 15	28 (21.5%)	28 (20.4%)	46 (37.4%)	102 (26.2%)	3 (4.4%)	6 (8.8%)	10 (15.9%)	19 (9.5%)
Day 22	35 (26.9%)	37 (27.0%)	54 (43.9%)	126 (32.3%)	2 (2.9%)	8 (11.8%)	11 (17.5%)	21 (10.6%)
Day 29	46 (35.4%	38 (27.7%)	65 (52.8%)	149 (38.2%)	4 (5.9%)	12 (17.6%)	11 (17.5%)	27 (13.6%)
Day 43	49 (37.7%)	44 (32.1%)	67 (54.5%)	160 (41.0%)	11 (16.2%)	14 (20.6%)	15 (23.8%)	40 (20.1%)

All three studies demonstrated statistical superiority to vehicle in the treatment of atopic dermatitis by day 15 (week 3) of the study ($p \leq 0.009$). Two of the three studies maintained superiority for the remainder of the studies, and one study, B307, maintained this superiority through day 22. This is important, for although, 6 weeks was the efficacy time point, given the nature of atopic dermatitis, with its discomfort and pruritus, realistically one would want to see significant improvement in the disease state within 2-3 weeks or patient compliance would be compromised.

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 included age, gender, race, 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 both males ($p = 0.002$) and females ($p < 0.001$). ASM 1% cream was statistically significantly better than vehicle in both White ($p < 0.001$) and non-White groups ($p < 0.001$). 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 ($p = 0.287$). See statistical review for full details.

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 data suggests that ASM 1% cream is equally effective in males and females, and across all ethnic groups. 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.

13 Overview of Safety

In some areas of the overview of safety, where appropriate, safety data will be separated by age, infants 3 months- 23 months, children 2-17 years of age, and adults.

13.1 Significant/Potentially Significant Events

In general, the most significant adverse events that can be attributed to ASM 1% cream are related to infections, primarily systemic. Other disorders noted in other systems where ASM 1% cream had a higher incidence, such as the pulmonary and gastrointestinal system may be interrelated to these infections.

Events occurring in the short term (over 6 weeks)

Ages 2-17 years

There were no statistically significant events that occurred at a higher rate in subjects using ASM 1% cream compared to vehicle.

These events occurred in a higher percentage (≥ 1%) of subjects using ASM 1% cream compared to vehicle. These included headache (13.9% vs. 8.8%), cough (11.6% vs. 8.1%), nasopharyngitis (10.1% vs. 7.4%), influenza (3.0% vs. 0.7%), otitis media (2.2% vs. 0.7%), nasal congestion (2.6% vs. 1.5%) and upper respiratory tract infection (14.2% vs. 13.2%) .

The incidence of application site burning was high in both arms, ASM 1% and vehicle, 10.4% and 12.5%. This adverse event was seen to decrease over time as only 1.5% of subjects complained of this in the open-label trial.

Ages 3 months – 23 months

These events occurred at a statistically significantly higher rate in subjects using ASM 1% cream compared to vehicle. These included pyrexia (31.7% vs. 12.7%), diarrhea (8.1% vs. 0%), and otitis media (4.1% vs. 0%).

These events occurred in a higher percentage (≥ 1%) of subjects using ASM 1% cream compared to vehicle. These included upper respiratory tract infection (23.6% vs. 14.3%), nasopharyngitis (14.6% vs. 7.9%), gastroenteritis (7.3% vs. 3.2%), teething (8.1% vs. 4.8%), restlessness (8.1% vs. 4.8%), asthma NOS (5.7% vs. 3.2%), and influenza (5.7% vs. 3.2%).

13.1.1 Other Significant/Potentially Significant Events

Events occurring in the open-label phase (20 weeks)

Ages 2-17 years

These events occurred at a higher percentage (≥ 1%) in the open-label phase in patients who had been on ASM 1% cream either over 26 weeks or 20 weeks as compared to the double-blind phase where patients had been on ASM 1% cream over a period of 6 weeks.

These events included nasopharyngitis (19.6% vs. 10.1%), upper respiratory tract infection (19.4% vs. 14.2%), pyrexia (12.2% vs. 7.5%), skin infection (5.4% vs. 3.0%), influenza (6.6% vs. 3.0%), ear infection (5.7% vs. 2.2%), asthma NOS (3.3% vs. 0.7%), asthma aggravated (3.9% vs. 1.5%), cough (11.6% vs. 9.3%), streptococcal pharyngitis (3.0% vs. 0.7%), sinusitis (3.3% vs. 1.1%), sore throat (5.4% vs. 3.4%), impetigo (3.6% vs. 1.9%), vomiting (4.2% vs. 3.0%), and rhinitis (1.5% vs. 0.4%).

Ages 3 months – 23 months

These events continued to occur at a high rate in the open-label phase for infants that continued on ASM 1% cream and those that switched from vehicle to ASM 1% cream. These included upper respiratory tract infection (21.4% vs. 21.4%), nasopharyngitis (13.7% vs. 21.4%), otitis media (9.4% vs. 7.1%), gastroenteritis (6.0% vs.8.9%), upper respiratory tract infection viral (2.6% vs. 5.4%), pyrexia (27.4% vbs. 26.8%), teething (10.3% vs. 8.9%), diarrhea (8.5% vs. 5.4%), and restlessness (8.5% vs. 7.1%).

Additional events that occurred at ≥ 2% in the infant study were bronchitis (9.2%), cough (8.1%), rhinitis (7.5%), tonsillitis (5.2%), dermatitis contact (4.4%), bacterial infection (3.5%), conjunctivitis (3.5%), ear infection (2.9%), molluscum contagiosum (2.9%), hypersensitivity (2.9%), food allergy (2.9%), chickenpox (2.3%), bronchospasm (2.3%), and vomiting (2.3%). Bronchitis acute, croup infectious, influenza, pneumonia, sinusitis, skin infection, influenza like illness, asthma, nasal congestion sore throat, erythema, skin lesion all occurred at 1.7% each.

Statistically significant events that occurred in the 1 year long term study, at the 6 month interim analysis of ASM 1% cream as compared to vehicle, to further support the poor safety profile in infants include hypersensitivity (8.3% vs. 2.2%), viral rash (4.4% vs. 0%), lower respiratory tract infection (3.9% vs. 0%), rhinorrhea (3.9% vs. 0%), wheezing (3.9% vs. 0%), toothache (2.9% vs. 9%), eye infection (2.5% vs. 0%), pharyngitis (2.5% vs. 0%), respiratory tract infection (2.5% vs. 0%), and irritability (2.5% vs. 0%).

Events occurring in the long term studies (1 year)

Ages 2-17 years

These events occurred in the ASM 1% cream subjects at ≥ 1% over the vehicle subjects. They include nasopharyngitis (26.5% vs. 21.3%), headache (25.4% vs. 16.0%), cough (15.8% vs. 10.7%), pyrexia (12.5% vs. 5.3%), influenza (13.2% vs. 4.0%), bronchitis (10.7% vs. 8.0%), application site burning (8.5% vs. 6.7%), pharyngitis (8.1% vs. 2.7%), sore throat (8.1% vs. 5.3%), gastroenteritis (7.4% vs. 2.7%), diarrhea (6.6% vs. 5.3%), tonsillitis (6.3% vs. 0%), viral infection (6.6% vs. 1.3%), asthma (3.7% vs. 2.7%), constipation (3.7% vs. <1%), epistaxis (3.3% vs. 1.3%), ear infection (3.3% vs. 1.3%), skin papilloma (3.3% vs. <1%), tonsillitis acute (2.6% vs. 0%), toothache (2.6% vs. 1.3%), application site erythema (2.2% vs. 0%), molluscum contagiosum (1.8% vs. 0%), upper respiratory tract infection viral (1.5% vs. 0), herpes simplex

dermatitis (1.5% vs. <1%), bronchitis acute (1.5% vs. 0%), bacterial infection 1.1% vs. 0%), and herpes zoster (1.1% vs. 0%).

Adults ≥ 18 years of age

Events that occurred in the adult study at ≥ 3% on ASM 1% cream included application site burning (25.9%), application site reaction (14.6%), influenza (9.8%), headache (7.0%), nasopharyngitis (7.6%), skin infection (6.4%), application site irritation (6.4%), application site pruritus (5.5%), folliculitis (6.1%), upper respiratory tract infection (4.3%), herpes simplex (4.0%), sore throat (3.7%), hypersensitivity (3.4%), conjunctivitis (3.0%), and eczema infected (3.0%).

13.1.2 Deaths

There were no deaths reported during the study period.

13.1.3 Overdose Experience

13.2 Other Safety Findings

Adverse events of special clinical interest will be discussed here and include the incidence of lymphadenopathy, eczema herpeticum (Kaposi's Varicelliform Eruption), herpes simplex, herpes zoster, and skin papilloma (warts).

There were 21 patients reporting lymphadenopathy or lymphadenitis, 13 patients in the original NDA (14 reports) and 8 patients in the 120-day safety update. Fourteen out 21 (67%) subjects were on ASM 1% cream and 7/21 (33%) subjects were on vehicle or active control (topical corticosteroid). The majority of cases were in the pediatric population, 15 (71%). Most of the cases were associated with infection and resolved during the study. For the few cases that did not resolve by end of study, they were associated with infection and patients discontinued secondary to non-therapeutic response. An exception to this was a 46 year old male with a right ear infection with right cervical adenopathy continuing 70 days after the start. This patient, however, was on active control. Nine of the pediatric cases occurred in the 1 year long term safety study and was the only study that had an incidence of greater than 1% [8/474 (1.7%)]. Again, though, all of the cases resolved except one patient who discontinued the study at day 43.

There were 14 cases of eczema herpeticum in the studies, 11 in the pediatric population and 3 in the adult population. All but one case was on ASM 1% cream. The majority of the pediatric cases (8, 72.7%) occurred in the 1 year long term safety trial with 4 of the cases occurring in subjects only on ASM 1% cream (4/272 or 1.5%) and 4 cases occurring in subjects with sequential use of ASM 1% cream and topical corticosteroid (4/202 or 2.0%). There was a small increase in incidence of eczema herpeticum when using ASM 1% cream (1.5% vs. 0%) and the incidence increases slightly with sequential use of topical corticosteroid (2.0% vs. 1.5%). The one vehicle case occurred in the same trial in a subject that used topical corticosteroid (1/162 or 0.6%). All of the cases resolved without sequelae and without recurrence during the period of

observation except one case that was uncomplicated but ongoing at the end of the study (study B316, the infant study).

There were 34 cases of herpes simplex infections in the studies, 21 cases in the pediatric population ages 2-17 years and 13 cases in adults. The majority of the pediatric cases, 17 occurred in the long term safety study, 13 in the ASM 1% cream arm (13/474) and 4 cases occurred in the vehicle arm (4/237). However, 4 cases in the ASM 1% cream arm also used topical corticosteroid and 2 cases in the vehicle arm used topical corticosteroid. Therefore, the actual incidence comparing ASM 1% cream to vehicle is 9/272 and 2/75 which gives and overall incidence difference of <1% (3.3% vs. 2.7%). The incidence does not increase with sequential use of topical corticosteroid (4/202 or 2.0% vs. 3.3% ASM 1% cream). Only one case occurred in the short-term vehicle controlled trial (1/267, 0.4%) and three cases in the open-label phase (3/335, 0.9%).

There were 4 cases of herpes zoster that occurred in patients on ASM 1% cream. All 4 cases occurred in the long-term safety trial (B313) in pediatric patients ages 2-17 years. Three of the cases occurred in the population only using ASM 1% cream (3/272, 1.1%) and one occurred in the population that also had sequential use of topical corticosteroid (1/202, 0.5%). There was 1 adult case while on ASM 1% cream (1/328, 0.3%) and 3 cases that occurred with topical corticosteroid (3/330, 0.9%).

There were 16 pediatric cases of papilloma (warts) observed. All but one patient was on ASM 1% cream. There were 3 cases in the short-term study B307 with a mean onset or worsening of the papilloma of 48 days. The youngest patient was 2 and the oldest was 12. There were 11 cases in trial B313 on ASM 1% cream but one can be discounted as it occurred after only 1 day of treatment. For the other 10 cases the mean drug days at onset of papilloma was 168.4 (24+ weeks) days, with the least being 14 days and the most was 329 days. The youngest child was 3 years old and the oldest was 15 years of age. This is compared to one case on vehicle – a 6 year old after 89 days of treatment. The comparable incidence rates were 10/474 (2.1%) for ASM 1% vs. 1/237 (0.4%) for vehicle. The once case that occurred in the infant trial (6 month interim analysis) occurred after only 1 day of treatment.

The sponsor was asked to provide an analysis of the effect of ASM 1% cream on growth velocity in children exposed to the drug product. The sponsor provided an analysis on study B313 and study 0315. Study B313 is a 1 year long term safety study in children, ages 2- 17 years old and study 0315 is a 6-month interim analysis of a 1 year long term safety study in infants 3 months – 23 months old. Standard height and weight curves were taken from the National Center of Health Statistics, issued October 16, 2000 since a similar document was not found for non-US populations (almost all the centers in these 2 studies were non-US centers). The percentile for each patient at each visit for height and weight was calculated. Weight was flagged as abnormally low if its percentile was <5.0 and as abnormally high if its percentile was >90.0. The same was done for height. Table 66 shows the results of this analysis for both studies, separately, and pooled.

Table 66
Frequency of Subjects with at least One Post-Baseline Value Of Height or Weight Outside the 90% Confidence Interval

Study		ASM 1%	Vehicle
ASMB 313		(N=474)	(N=237)
	Weight high	55 (11.6%)	32 (13.5%)
	Weight low	47 (9.9%)	17 (7.2%)
	Height high	64 (13.5%)	38 (16.0%)
	Height low	49 (10.3%)	18 (7.6%)
ASMB 315		(N= 204)	(N=46)
	Weight high	21 (10.3%)	5 (10.9%)
	Weight low	27 (13.2%)	9 (19.6%)
	Height high	42 (20.6%)	6 (13.0%)
	Height low	20 (9.8%)	5 (10.9%)
Pooled		(N=678)	(N=283)
	Weight high	76 (11.2%)	37 (13.1%)
	Weight low	74 (10.9%)	26 (9.2%)
	Height high	106 (15.6%)	44 (15.5%)
	Height low	69 (10.2%)	23 (8.1%)

The data presented here is limited in that these 2 studies include patients who also used topical corticosteroid cream and thus complicate the ASM 1% cream assessment. Further, the data fall short in that it does not assess the individual patients growth curve and its relationship to the patient's own growth pattern. The sponsor was unable to provide that information. Thus, definitive comments regarding the effect of ASM 1% cream on growth velocity cannot be made with this data.

13.2.1 ADR Incidence Tables

Pediatric Patients ages 2-17 years and Adults

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1-year)		Adult Active Comparator (1 year)
	ASM 1% (N=267) N (%)	Vehicle (N=136) N (%)	ASM 1% Cream (N=335) N (%)	ASM 1% (N=272) N (%)	Vehicle (N=75) N (%)	ASM 1% Cream (N=328) N (%)
At least 1 AE	182 (68.2%)	97 (71.3%)	240(72.0%)	230(84.6%)	56 (74.7%)	256 (78.0%)
Infections and infestations						
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (19.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	< 1%	0
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)
General disorders and administration site conditions						
Application Site Burning	28 (10.4)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	5 (1.1%)	3 (4.0%)	21 (6.4%)
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	18 (5.5%)
Respiratory, thoracic and mediastinal disorders						
Cough	31 (11.6)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	< 1%	< 1%	3 (0.9%)
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	< 1%	0
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)

	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)	Pediatric Patients* Vehicle-Controlled (1-year)		Adult Active Comparator (1 year)
	ASM 1% (N=267) N (%)	Vehicle (N=136) N (%)	ASM 1% Cream (N=335) N (%)	ASM 1% (N=272) N (%)	Vehicle (N=75) N (%)	ASM 1% Cream (N=328) N (%)
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)
Gastrointestinal disorders						
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)
Sore Throat	9 (3.4%)	5 (3.7%)	15 (5.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	18 (6.6%)	4 (5.3%)	7 (2.1%)
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	< 1%	0
Loose Stools	0	1 (0.7%)	4 (1.2%)	< 1%	< 1%	0
Reproductive System and Breast Disorders						
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)
Eye Disorders						
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)
Skin & Subcutaneous Tissue Disorders						
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (1.5%)	< 1%	3 (0,9%)
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)
Immune System Disorders						
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)
Injury and poisoning						
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1 %	1 (1.3%)	0
Laceration	2 (0.9%)	1 (0.7%)	5 (1.5%)	< 1%	< 1%	0
Musculoskeletal, Connective Tissue and Bone Disorders						
Back Pain						6 (1.8%)
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)
Ear and Labyrinth Disorders						
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.7%)	2 (2.7%)	0
Nervous system disorders						
Headache	37 (13.9)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)

* ages 2-17 years

Infants ages 3 months – 23 months

	ASM 1% Vehicle Controlled 6 weeks (N=123) N (%)	Vehicle Vehicle Controlled 6 weeks (N=63) N (%)	ASM 1% Cream Open Label 20 weeks (N=173)
At least 1 common AE	84 (68.3%)	39 (61.9%)	135 (78.0%)
Infections and infestations			
Upper respiratory tract Infection NOS	29 (23.6%)	9 (14.3%)	37 (21.4%)
Nasopharyngitis	18 (14.6%)	5 (7.9%)	28 (16.2%)
Gastroenteritis NOS	9 (7.3%)	2 (3.2%)	12 (6.9%)
Bronchitis NOS	7 (5.7%)	3 (4.8%)	16 (9.2%)
Influenza	7 (5.7%)	2 (3.2%)	3 (1.7%)
Otitis media NOS	5 (4.1%)	0	15 (8.7%)
Bacterial infection NOS	1 (0.8%)	4 (6.3%)	6 (3.5%)
Pharyngitis NOS	2 (1.6%)	2 (3.2%)	2 (1.2%)
Stye	2 (1.6%)	0	0
Tinea NOS	2 (1.6%)	0	0
Upper Respiratory Tract Infection Viral NOS	2 (1.6%)	0	6 (3.5%)
Sinusitus NOS	1 (0.8%)	1(1.6%)	3 (1.7%)
Scabies infestation	0	2 (3.2%)	0
Bronchopheumonia NOS	0	1(1.6%)	1 (0.6%)
Eye Infection Bacterial NOS	0	1(1.6%)	1 (0.6%)
Folliculitis	0	1(1.6%)	1 (0.6%)
Otitis Media Serous NOS	0	1(1.6%)	1 (0.6%)
Respiratory Tract Infection NOS	0	1(1.6%)	0
Rubella	0	1 (1.6%)	2 (1.2%)
Skin Infection NOS	0	1 (1.6%)	3 (1.7%)
Tonsillitis NOS	0	1 (1.6%)	9 (5.2%)
Molluscum Contagiousm	1 (0.8%)	0	5 (2.9%)
Chickenpox	0	0	4 (2.3%)
Bronchitis Acute NOS	0	0	3 (1.7%)
Croup	0	0	3 (1.7%)
Pneumonia	1 (0.8%)	1 (1.6%)	3 (1.7%)
Gastrointestinal Infection NOS	0	0	2 (1.2%)
Viral Infection NOS	1 (0.8%)	0	2 (1.2%)
General disorders and administration site conditions			
Pyrexia	39 (31.7%)	8 (12.7%)	47 (27.2%)
Application site irritation	0	3(4.8%)	0
Application Site Reaction NOS	2 (1.6%)	1(1.6%)	0
Application Site Burning	1(0.8%)	1(1.6%)	1 (0.6%)
Application Site Erythema	2 (1.6%)	0	0
Pain NOS	2 (1.6%)	0	0
Influenza Like Illness	0	1 (1.6%)	3 (1.7%)
Respiratory, thoracic and mediastinal disorders			
Rhinitis NOS	6 (4.9%)	5 (7.9%)	13 (7.5%)
Asthma NOS	7 (5.7%)	2 (3.2%)	3 (1.7%)
Cough	5 (4.1%)	3 (4.8%)	14 (8.1%)
Bronchospasm NOS	4 (3.3%)	3 (4.8%)	4 (2.3%)
Nasal congestion	3 (2.4%)	3 (4.8%)	3 (1.7%)
Rhinorrhea	4 (3.3%)	1 (1.6%)	2 (1.2%)
Chest Tightness	2 (1.6%)	0	1 (0.6%)
Wheezing	2 (1.6%)	0	1 (0.6%)
Asthma Aggravated	0	1 (1.6%)	1 (0.6%)
Gastrointestinal disorders			
Teething	10 (8.1%)	3 (4.8%)	17 (9.8%)
Diarrhea NOS	10 (8.1%)	0	13 (7.5%)

	ASM 1% Vehicle Controlled 6 weeks (N=123) N (%)	Vehicle Vehicle Controlled 6 weeks (N=63) N (%)	ASM 1% Cream Open Label 20 weeks (N=173)
Vomiting NOS	5 (4.1%)	3 (4.8%)	4 (2.3%)
Gingival Pain	2 (1.6%)	0	2 (1.2%)
Loose Stools	2 (1.6%)	0	0
Nausea	2 (1.6%)	0	0
Abdominal pain Upper	0	1 (1.6%)	2 (1.2%)
Psychiatric disorders			
Restlessness	10 (8.1%)	3 (4.8%)	14 (8.1%)
Irritability	1 (0.8%)	2 (3.2%)	0
Sleep Disorder NOS	2 (1.6%)	1 (1.6%)	0
Skin & subcutaneous tissue Disorders			
Dermatitis contact	4 (3.3%)	1 (1.6%)	7 (4.4%)
Pruritus	1 (0.8%)	1 (1.6%)	0
Urticaria	1 (0.8%)	1 (1.6%)	2 (1.2%)
Eyelid edema	0	1 (1.6%)	0
Rash Papular	0	1 (1.6%)	0
Erythema	1 (0.8%)	0	3 (1.7%)
Skin Lesion NOS	1 (0.8%)	0	3 (1.7%)
Dermatitis NOS	1 (0.8%)	0	2 (1.2%)
Heat Rash	0	0	2 (1.2%)
Skin Ulcer NOS	0	1 (1.6%)	0
Eye disorders			
Conjunctivitis NEC	2 (1.6%)	2 (3.2%)	6 (3.5%)
Immune System Disorders			
Food Allergy	2 (1.6%)	0	5 (2.9%)
Hypersensitivity	1 (0.8%)	1 (1.6%)	5 (2.9%)
Injury and poisoning			
Abrasion NOS	4 (3.3%)	0	0
Limb Injury NOS	2 (1.6%)	0	0
Head Injury	0	1 (1.6%)	0
Laceration	0	1 (1.6%)	1 (0.6%)
Nervous system disorders			
Headache	0	0	2 (1.2%)
Insomnia NEC	1 (0.8%)	2 (3.2%)	2 (1.2%)

13.2.2 Laboratory Findings, Vital Signs, ECGs

There were not any clinically significant out of range laboratory findings or vital signs that could be attributed to ASM 1% cream. There was a post-baseline increase in eosinophilia in both groups in the controlled short-term studies (B305, B307, and B316) of 4.3% for ASM 1% cream and 5.3% for vehicle. ECGs were not performed in these studies.

13.2.3 Special Studies

The topical dermal studies revealed a low cumulative irritancy potential when applied under exaggerated use conditions.

The results of skin anergy testing in a small subset of subjects ages 2-17 years of age did not reveal any adverse effect on the cellular immune system by ASM 1% cream.

13.2.4 Drug-Demographic Interactions

There were not any statistically significant differences in response to treatment with ASM 1% cream among age or sex. When grouped together non-Caucasians did not differ significantly from Caucasians in their response to treatment with ASM 1% cream. There were not enough elderly patients in the studies to make an analysis. Adult patients had a similar adverse event profile to that of pediatric patients, ages 2-17 years.

13.2.5 Drug-Disease Interactions

No other diseases were studied in these trials other than atopic dermatitis.

13.2.6 Drug-Drug Interactions

The use of topical corticosteroids used sequentially with ASM 1% cream was analyzed. The following are the statistically significant events that occurred when topical corticosteroid was used sequentially with ASM 1% cream as compared to ASM 1% cream along: impetigo (11.4% vs. 4.0%), skin infection (10.4% vs. 2.2%), rhinitis (9.4% vs. 4.4%), urticaria (5.0% vs. 0.4%), and superinfection (4.0% vs. 0.7%).

13.2.7 Withdrawal Phenomena/Abuse Potential

In an attempt to look at "rebound" phenomena as it relates to Elidel, a comparison of the incidence of aggravation of atopic dermatitis was analyzed. The incidences associated with preferred terms used to record aggravation of atopic dermatitis signs and symptoms ('condition aggravated', 'pruritus aggravated', 'dermatitis aggravated', and 'dermatitis NOS aggravated') were used to make this assessment.

Aggravation of atopic dermatitis was recorded as an adverse event in 28/1599 (1.75%) patients in the ASM 1% cream group and 17/897 (1.89%) patients in the control group. The incidence of aggravation of atopic dermatitis is essentially the same in both the drug product arm and vehicle arm. This suggests that ASM 1% cream is not associated with a "rebound" phenomenon in atopic dermatitis.

13.2.8 Human Reproduction Data

There were 7 pregnancies reported in the studies, 6 on ASM 1% cream and one on active control. The patient on active control was an adult who delivered a full-term healthy baby. Three pregnancies occurred in teenagers ages 15, 16, and 17 who had been on ASM 1% cream for a mean duration of 183 days (range 166-193 days). One teenager terminated her pregnancy, one had a full-term delivery of a healthy baby, and one had a spontaneous abortion after 4 months of treatment. Adult ages ranged from 24 years – 31 years of age. Two of the three remaining adults withdrew from the study and there is not any follow-up. These two subjects had been on study drug for a mean duration of 54 days. The remaining adult patient was on ASM 1% cream for

228 days and had a spontaneous abortion. The incidence of spontaneous abortions in this group is 33% (2/6 pregnancies) on ASM 1% cream.

This incidence is higher than would be expected for this age group and should range anywhere from 12% to 25% in the female population less than 40 years of age. The relationship to ASM 1% cream probably cannot be ascertained from such small numbers. The preclinical studies done with oral ASM 981did find that there was suppressed estrogen levels, disturbances of the estrous cycle and embryolethality (implantation loss) in female rats. This did not occur with dermal administration of the cream. However, the information is limited at best as the duration of exposure was 18 hours less a day than what is preferred (see pharm/tox review).

13.3 Safety Conclusions

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). This overview will separate the data of infants ages 3 months to 23 months from that of children ages 2-17 years of age. The data was reviewed in this manner because infants have a higher skin surface to body mass ratio and as ASM 1% cream is an immunosuppressant, the effects on infants may behave differently than in older children. Thus, it was important not to pool their safety data without assessing it separately at first. After review, in this reviewer's opinion, the data suggests a poorer safety profile in infants than it does in children or adults. Adult safety data will also be summarized separately. Thus in the studies for pediatric patients ages 2-17 years of age (studies B305, B307, and B313), the total number of patients treated with ASM 1% cream was 843 patients. Four hundred and eight patients were treated with vehicle in these studies. Study B316 and 0315, the infant studies, had 383 patients treated with ASM 1% cream and 109 patients were treated with vehicle in these 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.

The increase in restlessness in the short-term study and irritability in the long term trial seen in these infants on ASM 1% cream, might, in this reviewer's opinion, be reflective of headache that was observed in the older children on ASM 1% cream as infants would be less likely to be able to communicate such a symptom with clarity.

[ ]

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. Eczema herpeticum had the largest increase as compared to vehicle (1.5% vs. 0%). Herpes simplex and zoster had smaller differences (0.6%). 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 infection in adults over 1 year, although not compared to vehicle overall was similar, albeit lower, than in the pediatric population ages 2- 17 years old. The incidence of viral infections ranged from 1.8% (gastroenteritis) to 9.8% (influenza). There was more non-specified skin infection in adults (6.4% vs. 2.2%) and folliculitis (6.1% vs. 2.2%) but the incidence of herpes simplex was similar (4.0% vs. 3.3%). Thus, the safety profile in adults does not preclude the use of ASM 1% cream for the treatment of mild to moderate atopic dermatitis in adults.

The incidence of spontaneous abortions was increased in this patient population compared to the expected norm for this age group. The incidence was 2/6 or 33% when the expected ranges from 12% in females less than 20 years old and increases to 26% in females greater than 40 years of age (Williams Obstetrics, 20th Ed., 1997). However, the number of pregnancies is very small and in this reviewer's opinion, a definitive risk cannot be ascertained.

14 Conclusions

The data has demonstrated that ASM 1% cream, pimecrolimus, is efficacious in the treatment of mild to moderate atopic dermatitis in non-immunocompromised patients. Although the number of patients were small, ASM 1% cream was not efficacious in treating patients with severe atopic dermatitis or in those with a total body surface area of involvement that was greater than 60%. There is an increase in infections over the long-term use of this drug product. The majority of the infections were mild to moderate and resolved without complications. However, since atopic dermatitis is a remitting and relapsing disease that may last for years, patients will have to be monitored and appropriate warnings placed in the label. Furthermore, when the preclinical data is taken into consideration, until such a time that more is known about the drug in humans, ASM 1% cream should probably be used as second line therapy.

[ ]

15 Recommendations

It is recommended that pimecrolimus, ASM 1% cream, be approved as second line therapy for the indication of mild to moderate atopic dermatitis in non-immunocompromised patients 2 years of age and older ——— Recommended labeling changes to be found in the addendum of the review should be considered part of the approval of the drug product.

Denise Cook, M.D.
Medical Officer, Dermatology

cc: HFD-540
HFD-340
HFD-540/CSO/WrightM
HFD-540/CHEM/Pappas
HFD-520/MICRO/
HFD-540/PHARM/HillB
HFD-540/MO/CookD
HFD-880/Biopharm/GhoshT
HFD-725/Stats/FriedlinV
In DFS 11/06/01
Returned 11/28/01
Re-entered in DFS 11/29/01

For Concurrence Only:
HFD-540/Clinical TL/LukeM
HFD-540/DivDir/WilkinJ

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/s/

Denise Cook
11/29/01 02:01:07 PM
MEDICAL OFFICER

Markham Luke
11/29/01 02:16:41 PM
MEDICAL OFFICER
See also, separate Labeling Review. Also, post-marketing studies recommended
by primary reviewer on page 3 of review.

Jonathan Wilkin
11/29/01 06:14:01 PM
MEDICAL OFFICER
There is no evidence of an antipruritic effect independent of improvement of the atopic dermatitis. The proposed Phase 4 Commitments will be discussed with OPDRA before finalizing for discussion with sponsor.

Jonca Bull
12/6/01 03:42:34 PM
MEDICAL OFFICER