5.	David F. Butler, M.D.	505/Lubbock, TX 79430
6.	Lawrence A. Schachner, M.D.	506/Miami, Fl 33136
7.	Richard G.B. Langley, M.D.	507/Boston, MA 02114
8.	Matthew J. Stiller, M.D.	508/New York, NY 10032
9.	David Pariser, M.D.	509/Norfolk, VA 23507
10.	Mark Boguriewicz, M.D.	510/Denver, CO 80206
11.	Michael T. Jarratt, M.D.	511/Austin, TX 78759

Reviewer's Comment: *The protocol for this study is the same as that for study CASM B305. Therefore, certain sections will refer the reader to that study rather than repeat the same information.*

11.4.1.1 Objective/Rationale

Please refer to section 11.3.1.1, page 24

11.4.1.2 Design

Please refer to section 11.3.1.2, page 24

11.4.1.3 Protocol

Please refer to section 11.3.1.3, page 25

11.4.1.3.1 Population

Please refer to section 11.3.1.3.1, page 26

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11.4.1.3.2 Endpoints

Please refer to section 11.3.1.3.2, page 26

11.4.1.3.3 Statistical considerations

Please refer to section 11.3.1.3.3, page 29

11.4.1.4 Results

11.4.1.4.1 Populations enrolled/analyzed

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

At the time of this report, 11 subjects were ongoing in the open-label phase of the study. Open-label safety data covering a minimum of day 99 of the study is presented for these subjects. Table 15 denotes the subject disposition for both the double-blind and the open-label phase of the study.

Table 15
Subject Disposition – B307

Number of subjects	ASM 1%/ASM 1% N (%)	Vehicle/ASM 1% N (%)	Total N (%)
Screened	N/A	N/A	272
Randomized	137	68	205
Treated	137 (100.0)	68 (100.0)	205 (100.0)
Completed DB phase	123 (89.8)	54 (79.4)	177 (86.3)
Entered OL phase	121 (88.3)	54 (79.4)	175 (85.4)
Completed OL phase	100 (73.0)	41 (60.3)	141 (68.8)
Ongoing in OL phase	8 (5.8)	3 (4.4)	11 (5.4)

Denominator for percentages is the number of randomized subjects
N/A = not applicable, DB = double-blind, OL = open-label
Source: Post-text tables 7.1-3, 7.1-4 and 7.1-8

All subjects who completed the double-blind phase, except for 2 on ASM 1% cream, entered the open-label phase of the study. Subject 501/002's parent withdrew consent after the final double-blind visit and subject 504/002's parent withdrew consent due to time constraints and the blood draws (final blood draw for the double-blind phase was refused).

Table 16 describes patient discontinuations for the double-blind phase of the study and the reasons for discontinuation. The majority of discontinuations in the vehicle group was for unsatisfactory therapeutic effect and withdrawal of consent. In the ASM 1% cream arm the majority of discontinuations was for lost to follow-up, followed by withdrawal of consent.

Table 16
Subjects Discontinuations – Double-Blind Phase
ITT Population – B307

	ASM 1% (N=137) N (%)	Vehicle (N=68) N (%)	Total (N=205) N (%)
Completed	123 (89.8)	54 (79.4)	177 (86.3)
All discontinuations	14 (10.2)	14 (20.6)	28 (13.7)
Reason for discontinuation			
Adverse event (s)	3 (2.2)	2 (2.9)	5 (2.4)
Unsat. therap. effect	1 (0.7)	5 (7.4)	6 (2.9)
Protocol violation	0	1 (1.5)	1 (0.5)
Withdrawal of consent	4 (2.9)	4 (5.9)	8 (3.9)
Lost to follow up	6 (4.4)	2 (2.9)	8 (3.9)

Source: Post-text table 7.1-3

Table 17 shows the major protocol violations that occurred during the open-label phase of the study. The predominate reason in both groups was unsatisfactory therapeutic response. This was due to either no improvement or a worsening of their disease since the double-blind phase or the occurrence of an acute flare that was not controlled by study medication.

Table 17
Subject Discontinuation – Open-Label Phase
ITT Population – B307

	ASM 1%/ASM 1% (N=121)* N (%)	Vehicle/ASM 1% (N=54)* N (%)	Total (N=175) N (%)
Completed	100 (82.6)	41 (75.9)	141 (80.6)
Ongoing	8 (6.6)	3 (5.6)	11 (6.3)
All discontinuations	13 (10.7)	10 (18.5)	23 (13.1)
Reason for discontinuation			
AE(s)	2 (1.7)	0	2 (1.1)
Unsat. therap. effect	6 (5.0)	5 (9.3)	11 (6.3)
Withdrawal of consent	1 (0.8)	2 (3.7)	3 (1.7)
Lost to follow-up	3 (2.5)	3 (5.6)	6 (3.4)
Administrative problems	1 (0.8)	0	1 (0.6)

*N = number of subjects who completed double-blind phase and entered open-label phase
Source: Post-text table 7.1-4

Table 18 shows the major protocol violations that occurred during the double-blind phase of the study.

Table 18
Major Protocol Violations – Double-Blind Phase
ITT Population – B307

Major protocol violations	ASM 1% (N=137)		Vehicle (N=68)		Total (N=205)	
	N	(%)	N	(%)	N	(%)
Total protocol violations	34	(24.8)	24	(35.3)	58	(28.3)
Under-compliant[†]	23	(14.6)	13	(20.6)	36	(16.6)
Used anti-pruritic treatment[‡]	3	(2.2)	5	(7.4)	8	(3.9)
IGA score >3 at baseline	7	(5.1)	3	(4.4)	10	(4.9)
< 5% TBSA involvement at Baseline	11	(8.0)	3	(4.4)	14	(6.8)
Used topical steroids[#]	5	(1.5)	6	(8.8)	11	(5.4)
Used systemic steriods[#]	2	(1.5)	2	(2.9)	4	(2.0)
Missed more than 2 visits or had no post-baseline assessments	1	(0.7)	2	(2.9)	3	(1.5)
Used leukotriene antagonist[#]	1	(0.7)	1	(1.5)	2	(1.0)

[†]Missed >10% of doses during the double-blind phase of the study
[‡]Used to treat AD during double-blind phase of study (not stable dose at Baseline)
[#]Either within 1 week (topical steroids, leukotriene antagonists) or 1 month (systemic steroid) of Baseline visit or during double-blind phase of study.
Note: a subject who had more than one major protocol violation was counted in each category.
Source: Listing 7.2-1

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

A summary of the baseline demographics is presented in table 19. The only statistically significant difference at baseline is that more males were in the ASM 1% cream arm.

Table 19
Baseline Demographics
ITT Population – B307

Parameter	Units	ASM 1% (N=137)	Vehicle (N=68)	p-value
Age (years)	mean ± SD	6.7 ± 4.05	6.9 ± 4.29	0.844[†]
	range	1 -17	1 –17	
	median	6.0	7.0	
Age group (years)				
N (%)	<2	1 (0.7)	2 (2.9)	
	2-<12	113 (82.5)	56 (82.4)	
	12-<18	16 (16.8)	10 (14.7)	
Sex (n, %)	Male	77 (56.2)	27 (39.7)	0.037[‡]
	Female	60 (43.8)	41 (60.3)	
Race (n, %)	Caucasian	70 (51.1)	32 (47.1)	0.737[‡]
	Black	38 (27.7)	23 (33.8)	
	Oriental	5 (3.6)	1 (1.5)	
	Other	24 (17.5)	12 (17.6)	
Weight (kg)	mean ± SD	30.2 ± 19.2	31.3 ± 18.1	0.577[#]
	range	9 - 108	10 – 90	
Height (cm)	mean ± SD	121.7 ± 25.4	123.5 ± 26.00	0.291[#]
	range	82 - 186	79 – 178	

[†]Wilcoxon rank sum test
[‡]Fishers exact test
[#]Van Elteren test, stratified by age category
Source: Post-text tables 7.4-1a and 10.4-3a

Figure 2 shows the age distribution at randomization. The majority of patients (82.4%) were between the ages of 2-12.

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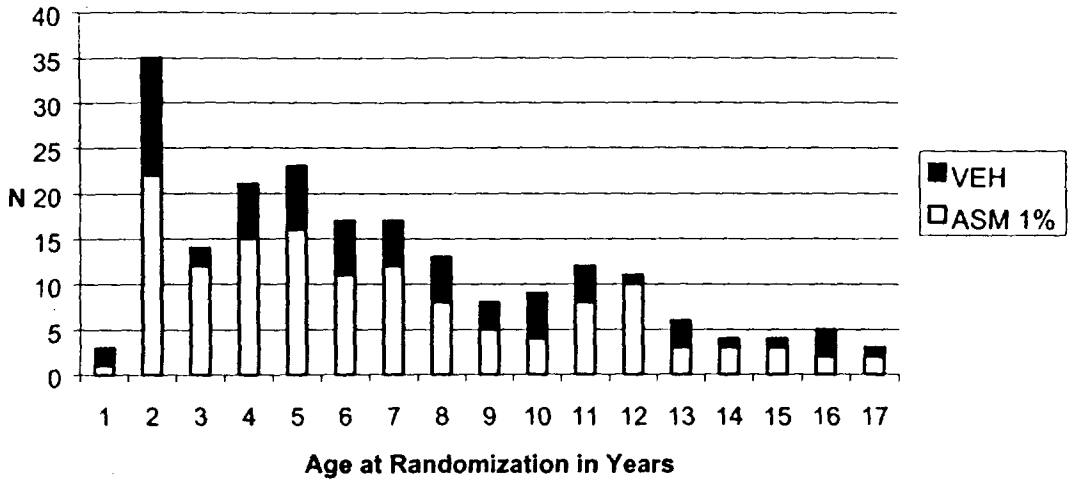
Figure 2
Age Distribution at Randomization
ITT Population – B307



Reviewer's Comment: *The majority of patients are in the younger age range which reflects that atopic dermatitis is primarily a disease of childhood. Specifically, 96 of the 205 (47%) patients enrolled in the study were ≤ 5 years of age and 69% (66/96) of the patients were in the ASM cream arm. Thus, there was an adequate representation of the youngest age group in the study on study medication.*

Table 20 shows the disease characteristics at baseline of the ITT population. There was no significant difference between vehicle and ASM 1% cream for any of the parameters.

Table 20
Disease Characteristics at Baseline
ITT Population – B307

Parameter	Units	ASM 1% (N=137) N (%)	Vehicle (N=68) N (%)	p-value
IGA score, N (%)	2 (mild)	52 (38.0)	25 (36.8)	0.953[†]
	3 (moderate)	78 (56.9)	40 (58.8)	
	4 (severe)	7 (5.1)	3 (4.4)	
% TBSA involved	<= 5%	11 (8.0)	7 (10.3)	0.389[‡]
	> 5% - <= 15%	55 (40.1)	20 (29.4)	
	> 15% - <= 30%	40 (29.2)	16 (23.5)	
	> 30% - <= 60%	19 (13.9)	23 (33.8)	
	> 60%	12 (8.8)	2 (2.9)	
		Mean ± SD range	**Mean ± SD range**	
% TBSA involved	overall	22.7 ± 20.0	23.6 ± 17.5	

[†]Mantel-Haenszel Chi-square test
Source: Post-text tables 7.4-3 to 7.4-5 and 9.2-9

Reviewer's Comment: *There is not a significant difference between arms in either the IGA score or % TBSA involvement. One hundred seventeen of the 205 subjects (57%) had a TBSA involvement of ≥ 15%. On further analysis, 55 out of 96 (57.3%) subjects ≤ 5 years of age had a %TBSA of ≥ 15% at baseline and 62/109 (56.9%) subjects ≥ 6 years of age had a %TBSA of ≥ 15% at baseline. This reflects an adequate population with moderate body surface area involvement.*

Each subject was supplied with 20 tubes of 50 g of study medication (1000 g total), with the assumption that subjects would require no more than 3 tubes per week during the double-blind phase. One patient (508/0001) from the ASM 1% group used all 20 tubes allotted for this phase and was re-supplied with 1 extra box (1000 g). This was an 11-year-old male who had moderate disease at baseline (IGA of 3), with approximately 68% TBSA affected. The mean treatment days of exposure to study medication during the double-blind phase was 40 days for ASM 1% cream and 37 days for vehicle. For the open-label phase the mean treatment days of exposure for ASM 1% cream and vehicle were 117 days and 112 days, respectively.

11.4.1.4.2 Efficacy endpoint outcomes

Treatment success was defined by the sponsor as an Investigator Global Assessment of "0" (clear) or "1" (almost clear) at day 43. Table 21 shows the treatment success.

Table 21
Treatment Success[1] – Investigator's Global Assessment
ITT Population – B307

Study period	ASM 1% (N=137)	Vehicle (N=68)	P-value[‡]
Baseline	0	0	
Day 8	13 (9.5%)	2 (2.9%)	0.091
Day 15	28 (20.4%)	6 (8.8%)	0.033
Day 22	37 (27.0%)	8 (11.8%)	0.009
Day 29	38 (27.7%)	12 (17.6%)	0.091
Day 43	44 (32.1%)	14 (20.6%)	0.076

[†]Defined as a score of 0 or 1 (clear or almost clear)
[‡]Derived from CMH test stratified by center
Source: Post-text tables 9.1-1 and 7.4-3

Reviewer's Comment: *There was a statistically significant difference between subjects in the ASM 1% cream and vehicle as early as day 15 (p=0.33), which was maintained through day 22 (p=0.009). Although statistical significance was not achieved at the sponsor's predetermined efficacy endpoint (day 43), a trend toward significance was maintained, such that progressively more subjects became clear or almost clear in the ASM 1% cream arm versus the vehicle arm (>than 10%). Atopic dermatitis is a disease in which one would want to observe significant clinical clearing of the disease within 2 weeks and at the most within 3 weeks or one risks patient compliance. This study does demonstrate statistical significance by those time points (2 and 3 weeks).*

The distribution of IGA scores by visit is presented in table 22. There was a statistical significance in the distribution of IGA scores at all post baseline visits.

Table 22
Frequency Distribution of IGA by Visit – Double-Blind Phase
ITT Population – B307

Visit[†] / Group	N	IGA score 0	1	2	3	4	5	p-value[‡]
Baseline								
ASM 1%	137	0	0	52 (38.0)	78 (56.9)	7 (5.1)	0	-
Vehicle	68	0	0	25 (36.8)	40 (58.8)	3 (4.4)	0	
Day 8								
ASM 1%	137	0	13 (9.5)	69 (50.4)	51 (37.2)	3 (2.2)	1 (0.7)	0.001
Vehicle	68	0	2 (2.9)	22 (32.4)	40 (58.8)	4 (5.9)	0	
Day 15								
ASM 1%	137	4 (2.9)	24 (17.5)	63 (46.0)	41 (29.9)	5 (3.6)	0	<0.001
Vehicle	68	0	6 (8.8)	18 (26.5)	38 (55.9)	6 (8.8)	0	
Day 22								
ASM 1%	137	6 (4.4)	31 (22.6)	53 (38.7)	44 (32.1)	3 (2.2)	0	<0.001
Vehicle	68	2 (2.9)	6 (8.8)	21 (30.9)	33 (48.5)	6 (8.8)	0	
Day 29								
ASM 1%	137	8 (5.8)	30 (21.9)	63 (46.0)	31 (22.6)	5 (3.6)	0	<0.001
Vehicle	68	3 (4.4)	9 (13.2)	20 (29.4)	28 (41.2)	7 (10.3)	1 (1.5)	
Day 43								
ASM 1%	137	15 (10.9)	29 (21.2)	55 (40.1)	35 (25.5)	3 (2.2)	0	0.002
Vehicle	68	5 (7.4)	9 (13.2)	19 (27.9)	28 (41.2)	7 (10.3)	0	

IGA categories: 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe, 5=Very Severe
[†]All non-missing post-Baseline values carried forward to all subsequent visits with missing data
[‡]CMH row mean score test, stratified by center
Source: Post-text table 9.1-2

Table 23 demonstrates the treatment success by baseline IGA and baseline %TBSA involved. Treatment by baseline IGA approached statistical significance.

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Table 23
Treatment success[†] by Baseline IGA and by Baseline %TBSA Involved
Double-Blind Phase – ITT Population – B307

	ASM 1% (N=137)		Vehicle (N=68)		
	N[‡] Baseline	N (%) successes	N[‡] Baseline	N (%) successes	P-value[‡]
Baseline IGA					
Overall	137	44 (32.1)	68	14 (20.6)	0.079
2	52	26 (50.0)	25	9 (36.0)	
3	78	17 (21.8)	40	5 (12.5)	
4 and 5	7	1 (14.3)	3	0 (0.0)	
Baseline %TBSA involved					
Overall	137	44 (32.1)	68	14 (20.6)	0.187
<= 5%	11	3 (27.3)	7	2 (28.6)	
> 5% - <= 15%	55	23 (41.8)	20	9 (45.0)	
> 15% - <= 30%	40	12 (30.0)	16	1 (6.3)	
> 30% - <= 60%	19	5 (26.3)	23	1 (4.3)	
> 60%	12	1 (8.3)	2	1 (50.0)	

[†]Defined as a score of 0 or 1
[‡]Number of subjects assessed
Source: Post-text tables 9.1-5 and 9.1-6

Reviewer's Comment: *ASM 1% cream does show a significant treatment effect for those patients who have at least moderate disease and those with more than 15% TBSA involved. There was a paucity of patients in the severe/very severe category and therefore a statistical analysis could not be made. However, from just descriptive statistics, only 1 out of 7 (14%) of those patients was a success. The same can be said for those subjects with >60% TBSA involvement. The success was very limited, 1 out of 12 (8.3%).*

Secondary signs and symptoms used to support the investigator's global assessment were erythema, induration/papulation, excoriation, lichenification, and pruritus. Table 24 shows the proportion of subjects with sign scores of 1 or less (mild or absent) for all the signs except pruritus.

Table 24
Number (%) of Subjects with Mild or Absent Key Signs of AD
ITT Population – B307

Visit	Treatment group	N	Erythema N (%)	Induration/ papulation N (%)	Excoriation N (%)	Lichenification N (%)
Double-blind phase						
Baseline	ASM 1%	137	47 (34.3)	50 (36.5)	71 (51.8)	68 (49.6)
	Vehicle	68	28 (41.2)	33 (48.5)	43 (63.2)	35 (51.5)
Day 15	ASM 1%	137	80 (58.4)	83 (60.6)	95 (69.3)	87 (63.5)
	Vehicle	68	26 (38.2)	30 (44.1)	43 (63.3)	33 (48.5)
Day 22	ASM 1%	137	81 (59.1)	93 (67.9)	95 (69.3)	93 (67.9)
	Vehicle		29 (42.6)	31 (45.6)	44 (64.7)	36 (52.9)
Day 43	ASM 1%	137	89 (65.0)	88 (64.2)	109 (79.6)	99 (72.3)
	Vehicle	68	34 (50.0)	36 (52.9)	44 (64.7)	40 (58.8)
Open-label phase						
Baseline[†]	ASM 1%/ASM 1%	121	80 (66.1)	79 (65.3)	96 (79.3)	88 (72.7)
	Vehicle/ASM 1%	54	30 (55.6)	32 (59.3)	37 (68.5)	34 (63.0)
Week 27	ASM 1%/ASM 1%	121	70 (57.9)	77 (63.6)	93 (76.9)	85 (70.2)
	Vehicle/ASM 1%	54	35 (64.8)	36 (66.7)	44 (81.5)	38 (70.4)

All body regions for the given sign with a score of 1 or less (mild or absent symptoms)
[†]Last double-blind assessment prior to entry into open-label phase
Source: Post-text tables 9.2-15 and 9.2-28

Reviewer's Comment: *In the key signs it can be seen that at days 15 and 22, there is a 17-20% difference in the number of patients who now have either mild or absent signs (corresponding with success) in the acute signs of atopic dermatitis, erythema and induration/papulation. This supports the statistical significance found between ASM 1% cream and vehicle in the investigator's global assessment at the same efficacy time points. There was a greater proportion of subjects with mild or absent signs for the more chromic signs, excoriation and lichenification, in the ASM 1% cream group than in the vehicle group at all post treatment time points. More significantly, the vehicle group started out with more patients at baseline who did not have significant findings for these 2 categories and remained relatively constant whereas the ASM 1% cream arm showed an increasing proportion of patients responding to treatment. At the end of the open-label phase both groups had similar results in all 4 signs which supports an ASM 1% cream effect on the disease process.*

Table 25 shows the frequency of the pruritus assessment.

Table 25
Frequency of Pruritus Assessment
ITT Population – B307

	Treatment group	N	0 Absent N (%)	1 Mild N (%)	2 Moderate N (%)	3 Severe N (%)	p-value† 0	p-value† 0, 1
Baseline	ASM 1%	137	0	18 (13.1)	62 (45.3)	57 (41.6)	N/A	0.198
	Vehicle	68	0	5 (7.4)	33 (48.5)	30 (44.1)		
Day 15	ASM 1%	137	9 (6.6)	66 (48.2)	39 (28.5)	23 (16.8)	0.800	<0.001
	Vehicle	68	4 (5.9)	15 (22.1)	29 (42.6)	20 (29.4)		
Day 43	ASM 1%	137	24 (17.5)	62 (45.3)	32 (23.4)	19 (13.9)	0.009	<0.001
	Vehicle	68	3 (4.4)	21 (30.9)	27 (39.7)	17 (25.0)		
Baseline*	ASM 1%/ ASM 1%	121	24 (19.8)	55 (45.5)	27 (22.3)	15 (12.4)	N/A	N/A
	Vehicle/ ASM 1%	54	3 (5.6)	19 (35.2)	20 (37.0)	12 (22.2)		
Week 27	ASM 1%/ ASM 1%	121	27 (22.3)	49 (40.5)	28 (23.1)	17 (14.0)	N/A	N/A
	Vehicle/ ASM 1%	54	10 (18.5)	27 (50.0)	8 (14.8)	9 (16.7)		

†p-value for pruritus score of 0 (absent) or 0, 1 (absent to mild) based on CMH general association test adjusted for center
*Baseline for the open-label is last double-blind assessment prior to entry into the open-label phase
N/A = not applicable
Source: Post-text tables 9.2-29 to 9.2-32

Reviewer's Comment: *Significantly more patients had an absence of or mild pruritus in the ASM 1% cream arm than vehicle from day 15 onward. This would correspond to the success that was noted at day 15 in the Investigator's Global Assessment. There was also a significant response at the efficacy time point, day 43 both for absence of pruritus and/or a combination of absent to mild pruritus ($p=0.009$ and $p<0.001$, respectively).*

Other signs that were observed for presence or absence were oozing/crusting, hyperpigmentation, hypopigmentation, and xerosis. Table 26 shows these results.

Table 26
Number (%) of Subjects with Additional Signs and Symptoms of AD at Endpoint
ITT Population

Visit	Treatment group	N[†]	Oozing/ crusting N (%)	Hyperpig-mentation N (%)	Hypopig-mentation N (%)	Xerosis N (%)	Other N (%)
Day 1	ASM 1%	135	53 (39.3)	66 (48.9)	88 (65.2)	124 (91.9)	42 (31.1)
	Vehicle	67	22 (32.8)	35 (52.2)	45 (67.2)	60 (89.6)	23 (34.3)
Day 43	ASM 1%	116	28 (24.1)	51 (44.0)	67 (57.8)	92 (79.3)	37 (31.9)
	Vehicle	51	18 (35.3)	31 (60.8)	31 (60.8)	42 (82.4)	20 (39.2)
Week 27	ASM 1%/ASM 1%	96	25 (26.0)	37 (38.5)	40 (41.7)	65 (67.7)	24 (25.0)
	Vehicle/ASM 1%	40	10 (25.0)	18 (45.0)	18 (45.0)	25 (62.5)	10 (25.0)

[†]Number of subjects assessed
Source: Post-text tables 9.2-70 and 9.2-71

Reviewer's Comment: *The change in oozing/crusting is the most significant as it reflects an acute sign of atopic dermatitis. The ASM 1% cream group had a decrease from baseline to endpoint of 15.2% whereas vehicle increased by 3.5%.*

11.4.1.4.3 Conclusions Regarding Efficacy Data

Study B307 is supportive of the claim that SDZ ASM 981 1% cream is superior to vehicle in the treatment of atopic dermatitis in children ages 2-17 years who had mild to moderate disease. Although statistical significance was not reached at day 43, it did approach significance (p=0.076) and there was numerical superiority of ASM 1% cream over vehicle by 11.5%. ASM 1% cream did reach statistical significance at day 15, end of week 2 (p=0.033), in the Investigator's Global Assessment. This effect was maintained for another week of treatment, p=0.009, at the end of week 3. The secondary efficacy parameters support this conclusion.

11.4.1.5 Safety outcomes

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

11.4.2 Combined Safety for Studies B305 and B307

Study B305 and B307 had identical protocols assessing the safety of ASM 1% cream in pediatric patients ages 2 – 17 years of age with mild to moderate atopic dermatitis. The ITT population for the double-blind phase of the combined studies consisted of 403 patients, 267 in the ASM 1% cream arm and 136 in the vehicle arm. The distribution of patients in both studies

were very similar, with the ASM 1% cream arm in study B307 having 7 more patients than in study B305. No statistical adjustment was made for this minor difference (after conferring with Dr. Freidlin, the biostatistician). The open-label phase of the studies had 233 patients who remained on ASM 1% cream and 102 patients who switched from vehicle to ASM 1% cream for a total of 335 patients on ASM 1% cream in the open-label phase of the studies combined. No statistical adjustment was made for the open-label phases of the studies because the difference here was also very small.

Most of the adverse events were mild to moderate in severity in both phases of the studies. In the double-blind phase of the studies, the severe reactions included one case each of application site burning, pneumonia, and eye infection on ASM 1% cream [3/267 (1.1%)]. The severe events on vehicle were 3 cases of application site burning, 2 cases of application site irritation, and one case each of application site reaction NOS, croup infectious, pneumonia, pruritus NOS, and dehydration [10/136 (7.4%)]. In the open-label phase of the studies, severe adverse events accounted for 3.6% (12/335) of all adverse events. These included 2 cases of pneumonia and asthma, and one case each of bacterial infection, herpes simplex dermatitis (Kaposi's Varicelliform Eruption), asthma aggravated, application site reaction, application site pruritus, application site irritation, laceration, and anaphylactic reaction to cefzil.

Discontinuations for adverse events were low in the studies. Nine subjects discontinued in the double-blind phase of the studies, 5 on the ASM 1% cream arm and 4 on the vehicle arm. This was due to local adverse events, application site problem or skin infection (bacterial). Four subjects discontinued the open-label phases of the studies, one for moderate application site reaction, one for moderate application site irritation, one for condition aggravated, and one for lupus nephritis. The lupus nephritis was not considered drug induced as the patient had baseline abnormalities that suggested the condition pre-existed.

Table 27 shows the incidence of common adverse events that occurred in ≥1% of the safety population for the double-blind phase of the study.

Table 27
Common Adverse Events (≥1%) Studies B305 and B307 Combined
Double - Blind Phase

	ASM 1% (N=267) N (%)	Vehicle (N=136) N (%)	Treatment difference & selected p values
At least 1 AE	182 (68.2%)	97(71.3%)	-3.1% p=0.52
At least 1 common AE	171 (64.0%)	97(71.0%)	-7% p=0.14
Infections and Infestations			
Upper Respiratory Tract Infection NOS	38 (14.2%)	18 (13.2%)	
Nasopharyngitis	27 (10.1%)	10 (7.4%)	2.7% p=0.35
Skin Infection	8 (3.0%)	9 (5.1%)	-2.1% p=0.10
Influenza	8 (3.0%)	1 (0.7%)	2.3% p=0.28
Ear Infection NOS	7 (2.6%)	2 (1.5%)	
Otitis Media	6 (2.2%)	1 (0.7%)	
Impetigo	5 (1.9%)	3 (2.2%)	
Bacterial Infection	4 (1.5%)	3 (2.2%)	
Folliculitis	3 (1.1%)	1 (0.7%)	
Sinusitis	3 (1.1%)	1 (0.7%)	
Pneumonia NOS	3 (1.1%)	1 (0.7%)	
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	

	ASM 1% (N=267) N (%)	Vehicle (N=136) N (%)	Treatment difference & selected p values
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	
Gastroenteritis	0	3 (2.2%)	-2.2% p=0.04
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	-3.3% p=0.02
Bronchitis	1 (0.4%)	3 (2.2%)	
General disorders and administration site conditions			
Application Site Burning	28 (10.4%)	17 (12.5%)	-2.1% p=0.55
Pyrexia	20 (7.5%)	12 (8.8%)	
Application Site Reaction NOS	8 (3.0%)	7 (5.1%)	-2.1% p=0.55
Application Site Irritation	8 (3.0%)	8 (5.9%)	-2.9% p=0.29
Application Site Pruritus	3 (1.1%)	2 (1.5%)	
Respiratory, thoracic and mediastinal disorders			
Cough	31 (11.6%)	11 (8.1%)	3.5% p=0.27
Nasal Congestion	7 (2.6%)	2 (1.5%)	
Rhinorrhea	5 (1.9%)	1 (0.7%)	
Asthma Aggravated	4 (1.5%)	3 (2.2%)	
Sinus Congestion	3 (1.1%)	1 (0.7%)	
Gastrointestinal disorders			
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	
Sore Throat	9 (3.4%)	5 (3.7%)	
Vomiting NOS	8 (3.0%)	6 (4.4%)	
Diarrhea NOS	3 (1.1%)	1 (0.7%)	
Nausea	1 (0.4%)	3 (2.2%)	
Gastrointestinal Upset	1 (0.4%)	2 (1.5%)	
Reproductive System and Breast Disorders			
Dysmenorrhea	3 (1.1%)	0	
Skin & Subcutaneous Tissue Disorders			
Urticaria	3 (1.1%)	0	
Pruritus NOS	1 (0.4%)	2 (1.5%)	
Smarting	0	3 (2.2%)	
Acne Aggravated	0	2 (1.5%)	
Eyelid Edema	0	2 (1.5%)	
Immune System Disorders			
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	
Injury and poisoning			
Accident NOS	3 (1.1%)	1 (0.7%)	
Musculoskeletal, Connective Tissue and Bone Disorders			
Back Pain	1 (0.4%)	2 (1.5%)	
Nervous system disorders			
Headache	37 (13.9%)	12 (8.8%)	5.1% p=0.13

Source: Post-text table 10.1-28, Volumes 1.157 and 1.172

Reviewer's Comment: *Overall, more adverse events occurred in the vehicle arm as compared to the ASM 1% cream arm, 71% and 64%, respectively. This was primarily due to local adverse events, such as skin infection, including staphylococcal infection, and local reactions to the vehicle. Gastroenteritis was also responsible for this increase. The vehicle group thus also had a slight increase over ASM 1% cream in the incidence of pyrexia (1.3%). This might be expected in the vehicle group given that patients with atopic dermatitis in this group, without medical treatment would have a compromise of skin integrity for a more sustained period than those being treated with active drug product.*

Application site burning was high in both groups, 10.4% for those on ASM 1% cream and 12.5% for those on vehicle. The reaction was defined as transient if it resolved within 7

days. This was the case for 41.3% of those on ASM 1% cream and 40% of those on vehicle. Although the non-transient cases were in the majority, the medication was well tolerated as only one subject discontinued from the ASM arm and 2 from the vehicle arm because of this adverse event in the double-blind phase of the study.

There were a few adverse events that occurred at a greater incidence in the ASM 1% cream arm than in the vehicle arm. Although there was not any statistical significance found between ASM 1% cream and vehicle for these events, those that had a difference of >1% in decreasing order of frequency were headache (ASM 13.9%, vehicle 8.8%), cough (ASM 11.6%, vehicle 8.1%), nasopharygitis (ASM 10.1%, vehicle 7.4%), influenza (ASM 3.0%, vehicle 0.7%), rhinorrhea (ASM 1.9%, vehicle 0.7%), and nasal congestion (ASM 2.6%, vehicle 1.5%).

There were not any clinically significant differences between ASM Cream 1% and vehicle in hematology, general chemistry, urine, or vital sign parameters.

Table 28 shows the incidence of common adverse events that occurred in ≥1% of the safety population in the open-label phase of the study.

Table 28
Incidence of Common Adverse Events ≥1% Studies B305 and B307 Combined Open-Label Phase

	ASM 1% (N=233) N (%)	Vehicle (N=102) N (%)	Treatment difference & selected p values
At least 1 AE	169 (72.5%)	71(70.0%)	2.5% p=0.59
Infections and infestations			
Upper Respiratory Tract Infection NOS	46 (19.7%)	19 (18.6%)	
Nasopharyngitis	26 (11.2%)	6 (5.9%)	5.3% p=0.12
Influenza	17 (7.3%)	5 (4.9%)	2.4% p=0.40
Ear Infection NOS	13 (5.6%)	6 (5.9%)	
Skin Infection	13 (5.6%)	5 (4.9%)	
Pharyngitis Streptococcal	10 (4.3%)	0	4.3% p=0.03
Impetigo NOS	10 (4.3%)	2 (2.0%)	2.3% p=0.35
Sinusitis	9 (3.9%)	2 (2.0%)	
Otitis Media	6 (2.6%)	4 (3.9%)	
Staphylococcal Infection NOS	6 (2.6%)	1 (1.0%)	
Bronchitis NOS	3 (1.3%)	1 (1.0%)	
Pneumonia NOS	3 (1.3%)	2 (2.0%)	
Bacterial Infection	2 (0.9%)	2 (2.0%)	
Chickenpox	3 (1.3%)	0	
Folliculitis	3 (1.3%)	0	
Herpes Simplex	4 (1.7%)	0	
Pharyngitis NOS	3 (1.3%)	0	
Tonsillitis	3 (1.3%)	0	
Urinary Tract Infection	1 (0.4%)	2 (2.0%)	
Body Tinea	1 (0.4%)	1 (1.0%)	
Herpes Simplex Dermatitis (KVE)[1]	0	1 (1.0%)	
Molluscum Contagiosum	1 (0.4%)	3 (3.0%)	
Tooth Abscess	3 (1.3%)	0	
Upper Respiratory Tract Infection Viral NOS	3 (1.3%)	0	
Viral Infection NOS	0	1 (1.9%)	
General disorders and administration site conditions			
Pyrexia	29 (12.4%)	12 (11.8%)	

	ASM 1% (N=233) N (%)	Vehicle (N=102) N (%)	Treatment difference & selected p values	
Application Site Reaction NOS	5 (2.1%)	2 (2.0%)		
Application Site Burning	4 (1.7%)	1 (1.0%)		
Application Site Irritation	1 (0.4%)	2 (2.0%)		
Application Site Pruritus	1 (0.4%)	1 (1.0%)		
Influenza like Illness	1 (0.4%)	1 (1.0%)		
Respiratory, thoracic and mediastinal disorders				
Cough	20 (8.6%)	11 (10.8%)	-2.2%	p=0.61
Asthma Aggravated	6 (2.6%)	7 (6.9%)	-4.3%	p=0.07
Asthma NOS	7 (3.0%)	4 (3.9%)		
Rhinitis	3 (1.3%)	2 (2.0%)		
Nasal Congestion	5 (2.1%)	1 (1.0%)		
Wheezing	4 (1.7%)	0		
Rhinorrhea	2 (0.9%)	1 (1.0%)		
Sinus Congestion	1 (0.4%)	1 (1.0%)		
Gastrointestinal disorders				
Sore Throat	12 (5.2%)	3 (2.9%)	2.3%	p=0.57
Vomiting NOS	6 (2.6%)	8 (7.8%)	-5.2%	p=0.04
Abdominal Pain Upper	4 (1.7%)	6 (5.9%)		
Abdominal Pain NOS	4 (1.7%)	1 (1.0%)		
Loose Stools	3 (1.3%)	1 (1.0%)		
Nausea	2 (0.9%)	2 (2.0%)		
Diarrhea NOS	0	2 (2.0%)		
Constipation	0	2 (2.0%)		
Toothache	1 (0.4%)	1 (1.0%)		
Vomiting Aggravated	0	1 (1.0%)		
Gastrointestinal Upset	0	1 (1.0%)		
Reproductive System and Breast Disorders				
Dysmenorrhea	5 (2.1%)	0		
Blood and lymphatic system disorders				
Lymphadenopathy	1 (0.4%)	1 (1.0%)		
Eye Disorders				
Conjunctivitis NEC	5 (2.1%)	2 (2.0%)		
Skin & Subcutaneous Tissue Disorders				
Dermatitis NOS	2 (0.9%)	1 (1.0%)		
Eyelid Edema	1 (0.4%)	1 (1.0%)		
Immune System Disorders				
Hypersensitivity NOS	11 (4.7%)	5 (4.9%)		
Seasonal Allergy	1 (0.4%)	2 (2.0%)		
Allergies Aggravated	1 (0.4%)	1 (1.0%)		
Injury and Poisoning				
Laceration	4 (1.7%)	1 (1.0%)		
Musculoskeletal, Connective Tissue and Bone Disorders				
Pain in Limb	2 (0.9%)	2 (2.0%)		
Neck Stiffness	0	1 (1.0%)		
Arthralgia	0	1 (1.0%)		
Nervous system disorders				
Headache	28 (12.0%)	10 (9.8%)	2.2%	p=0.55
Sinus Headache	1 (0.4%)	1 (1.0%)		
Dizziness (exc vertigo)	0	1 (1.0%)		
Syncope	0	1 (1.0%)		
Psychiatric Disorders				
Depression	1 (0.4%)	1 (1.0%)		

Source: Post-text table 10.1-13 Volumes 1-157 and 1-172

Reviewer's Comment: *In the analysis of the open-label phase of the study, one wants to ascertain if there was a general rise in any particular adverse event over time (20-26 weeks) as compared to the double-blind phase (6 weeks) and if adverse events in the vehicle arm tended to approach those of ASM 1% cream, where applicable. Table 28 shows that overall, the incidence of adverse events rose over time and that there is not much difference between using the drug for 26 weeks (ASM 1% arm) or for 20 weeks (vehicle arm). An exception to this is the incidence of streptococcal pharyngitis (4.3% ASM, 0 vehicle; p=0.034).*

The rise in adverse events over time is more easily discernable in table 29, where all subjects from the open label phase are combined and compared with the ASM 1% arm of the double-blind phase for events that occurred ≥1%. Vehicle subjects from the double-blind phase are included for reference.

Table 29
Comparison of Common Adverse Events (≥1%) on ASM 1% Cream
Double-Blind Phase, Open-Label Phase, and on Vehicle
Studies 305 and 307 Combined (Safety Population)

	ASM 1% (DB)[1] (N=267) N (%)	ASM 1% (OL)[2] (N=335) N (%)	Vehicle (DB)[1] (N=136) N (%)
At least 1 AE	182 (68.2%)	240(72.0%)	97(71.3%)
Infections and infestations			
Total	102 (38.2%)	178 (53.0%)	59 (43.4%)
Upper Respiratory Tract Infection NOS	38 (14.2%)	65 (19.4%)	18 (13.2%)
Nasopharyngitis	27 (10.1%)	32 (19.6%)	10 (7.4%)
Skin Infection	8 (3.0%)	18 (5.4%)	9 (5.1%)
Influenza	8 (3.0%)	22 (6.6%)	1 (0.7%)
Ear Infection NOS	6 (2.2%)	19 (5.7%)	2 (1.5%)
Otitis Media	6 (2.2%)	10 (3.0%)	1 (0.7%)
Impetigo NOS	5 (1.9%)	12 (3.6%)	3 (2.2%)
Bacterial Infection	1 (1.5%)	4 (1.2%)	3 (2.2%)
Folliculitis	3 (1.1%)	3 (0.9%)	1 (0.7%)
Sinusitis	3 (1.1%)	11 (3.3%)	1 (0.7%)
Pneumonia NOS	3 (1.1%)	5 (1.5%)	1 (0.7%)
Pharyngitis Streptococcal	2 (0.7%)	10 (3.0%)	2 (1.5%)
Molluscum Contagiosum	2 (0.7%)	4 (1.2%)	0
Staphylococcal Infection NOS	1 (0.4%)	7 (2.1%)	5 (3.7%)
Bronchitis NOS	1 (0.4%)	4 (1.2%)	3 (2.2%)
Herpes Simplex	1 (0.4%)	4 (1.2%)	0
General disorders and administration site conditions			
Total	57 (21.3%)	59 (17.6%)	29 (21.3%)
Application Site Burning	28 (10.4%)	5 (1.5%)	17 (12.5%)
Pyrexia	20 (7.5%)	41 (12.2%)	12 (8.8%)
Application Site Reaction NOS	8 (3.0%)	7 (2.1%)	7 (5.1%)
Application Site Irritation	8 (3.0%)	3 (0.9%)	8 (5.9%)
Application Site Pruritus	3 (1.1%)	2 (0.6%)	2 (1.5%)
Respiratory, thoracic and mediastinal disorders			
Total	46 (17.2%)	63 (18.8%)	16 (12.0%)
Cough	31 (11.6%)	31 (9.3%)	11 (8.1%)

	ASM 1% (DB)[1] (N=267) N (%)	ASM 1% (OL)[2] (N=335) N (%)	Vehicle (DB)[1] (N=136) N (%)
Nasal Congestion	7 (2.6%)	6 (1.8%)	2 (1.5%)
Rhinorrhea	5 (1.9%)	3 (0.9%)	1 (0.7%)
Asthma Aggrevated	4 (1.5%)	13 (3.9%)	3 (2.2%)
Sinus Congestion	3 (1.1%)	2 (0.6%)	1 (0.7%)
Asthma NOS	2 (0.7%)	11 (3.3%)	1 (0.7%)
Rhinitis	1 (0.4%)	5 (1.5%)	0
Wheezing	1 (0.4%)	4 (1.2%)	1 (0.7%)
Gastrointestinal disorders			
Total	35 (13.1%)	47 (14.0%)	22 (16.2%)
Abdominal Pain Upper	11 (4.1%)	10 (3.0%)	6 (4.4%)
Sore Throat	9 (3.4%)	15 (5.4%)	5 (3.7%)
Vomiting NOS	8 (3.0%)	14 (4.2%)	6 (4.4%)
Diarrhea NOS	3 (1.1%)	2 (0.6%)	1 (0.7%)
Nausea	1 (0.4%)	4 (1.2%)	3 (2.2%)
Abdominal Pain NOS	1 (0.4%)	5 (1.5%)	1 (0.7%)
Looses Stools	0	4 (1.2%)	1 (0.7%)
Reproductive System and Breast Disorders			
Total	5 (1.9%)	5 (1.5%)	2 (1.5%)
Dysmenorrhea	3 (1.1%)	5 (1.5%)	0
Eye Disorders			
Total	6 (2.2%)	10 (3.0%)	2 (1.5%)
Conjunctivitis NEC	2 (0.7%)	7 (2.1%)	1 (0.7%)
Skin & Subcutaneous Tissue Disorders			
Total	12 (4.5%)	17 (5.1%)	11 (8.1%)
Urticaria	3 (1.1%)	1 (0.3%)	0
Immune System Disorders			
Total	17 (6.4%)	25 (7.5%)	7 (5.1%)
Hypersensitivity NOS	11 (4.1%)	16 (4.8%)	6 (4.4%)
Injury and Poisoning			
Total	10 (3.7%)	20 (6.0%)	5 (3.7%)
Accident NOS	3 (1.1%)	1 (0.3%)	1 (0.7%)
Laceration	2 (0.9%)	5 (1.5%)	1 (0.7%)
Nervous system disorders			
Total	39 (14.6%)	41 (12.2%)	14 (10.3%)
Headache	37 (13.9%)	38 (11.3%)	12 (8.8%)

Source: Adapted from post-text tables 10.1-13 Volumes 1-157 and 1-172 and 10.1-28 Volumes 1-157 and 1-172

[1]Double-Blind – 6weeks

[2]Open-Label – 20 weeks

Reviewer's Comment: *There were several adverse events that increased when ASM 1% cream was used up to 26 weeks as compared to 6 weeks. Those with a ≥2% difference were upper respiratory tract infection NOS (19.4% vs. 14.2%), nasopharyngitis (19.6% vs. 10.1%), pyrexia (12.2% vs. 7.5%), asthma aggravated (3.9% vs. 1.5%), asthma NOS (3.3%, 0.7%), skin infection (5.4% vs. 3.0%), influenza (6.6% vs. 3.0%), sore throat (5.4% vs. 3.4%), ear infection (5.7% vs. 2.2%), sinusitis (3.3% vs. 1.1%), and streptococcal pharyngitis (3.0% vs. 0.7%).*

11.5 Sponsor's protocol # CASM981 0316

Title: "A 26-week Study With a 6-week Randomized, Multicenter, Double-Blind, Vehicle-Controlled, Parallel-Group Phase followed by a 20-week Open-Label Phase to Study the Safety and Efficacy of 1% SDZ ASM 981 Cream in Pediatric Subjects with Atopic Dermatitis"

11.5.1 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. Only 1 site, ——— has not responded to provide financial disclosure information as of 9/12/01.

11.5.2 Investigators

1.	A. Halbert, M.D.	101/Perth, WA, Australia
2.	Silmara Pereira, M.D.	201/São Paulo, Brazil
3.	Alonso Fausto Forin, M.D.	202/São Paulo, Brazil
4.	Roberto Takaoka, M.D.	203/São Paulo, Brazil
5.	Mario Cezar Pires, M.D.	204/São Paulo, Brazil
6.	Aditya Gupta, M.D.	301/London, Ontario, Canada
7.	Vincent Ho, M.D.	302/CAN-Vancouver, Canada
8.	Charles Lynde, M.D.	303/Markham, Ontario, Canada
9.	Kim Papp, M.D.	304/East Waterloo, ON, Canada
10.	Roland Kaufmann, M.D.	401/Frankfurt, Germany
11.	Regina Foelster-Holst, M.D.	402/Kiel, Germany
12.	Peter Hoeger, M.D., PhD	403/Hamburg, Germany
13.	Klaus Deichmann, M.D.	404/Freiburg, Germany
14.	Henning Hamm, M.D.	405/Würzburg, Germany
15.	Marcelle Groenewald, M.B.Ch.B	701/Thaba Tshwane, South Africa
16.	P.M. Jeena, M.B.Ch.B	702/Durban, South Africa
17.	D.N. Patel, M.B.Ch.B	703/Johannesburg, South Africa
18.	Paul Potter, M.B.Ch.B	704/Cape Town, South Africa
19.	Noufal Raboobee, M.B.Ch.B	705/Durban, South Africa
20.	Schalk Reyneke, M.B.Ch.B	707/Johannesburg, South Africa
21.	Gail Todd, M.B.Ch.B	708/Cape Town, South Africa
22.	Mariano Casado Jiménez, M. D.	802/Madrid, Spain
23.	J.M. Hernanz Hermosa, M.D.	803/Madrid, Spain
24.	Francisco Vanaclocha Sebastián, M.D.	804/Madrid, Spain
25.	Jerónimo Escudero Ordóñez, M.D.	805/Sevilla, Spain

11.5.1.1 Objective/Rationale

According to the sponsor, the following were the objectives of the study:

Primary objective:
To demonstrate superior efficacy of 1% SDZ ASM 981 cream compared to vehicle after 6 weeks double-blind treatment in pediatric subjects ages 3 – 23 months with mild to moderate atopic dermatitis.
Secondary objectives:
• To determine safety and tolerability of 1% SDZ ASM 981 cream treatment for up to 26 weeks;
• To evaluate the efficacy of 1% SDZ ASM 981 cream versus vehicle when treating the head and neck after 6 weeks double-blind treatment;
• To monitor the continued effect of 1% SDZ ASM 981 cream in the management of atopic dermatitis when used uncontrolled for up to an additional 20 weeks (Note: Uncontrolled refers to treatment with active medication without the use of a comparator);
• To compare the quality of life indices of subjects' caregivers after 6 weeks double-blind treatment.

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

11.5.1.2 Design

This 26-week multicenter study was divided into two treatment phases. A 6-week double-blind phase with a 2:1 randomization (active to vehicle) evaluated the efficacy and safety effects of treatment on infant subjects, *ages 3-23 months*, with mild to moderate atopic dermatitis. After completing the double-blind phase, achieving clearance of disease as evaluated by the investigator, or experiencing unsatisfactory therapeutic response after 3 weeks of double-blind treatment, subjects were allowed to enter a 20-week uncontrolled open-label phase that evaluated efficacy and safety of SDZ ASM 981 cream 1%.

11.5.1.3 Protocol

There were 2 criteria, one each in the inclusion and exclusion criteria that were different from the other two pivotal trials. Refer to section 11.3.1.3, page **25** for the other inclusion/exclusion criteria.

Inclusion Criteria:

Of any sex or race, between the ages of 3 and 23 months, with written consent of the legal guardian

Exclusion Criteria:

Subjects who were being breastfed by women taking prohibited medications/treatments

11.5.1.3.1 Population

The study population was comprised of pediatric subjects ages 3 months to 23 months who had mild to moderate atopic dermatitis affecting at least 5% of their total body surface area (TBSA).

11.5.1.3.2 Endpoints

Please refer to section 11.3.1.3.2, page 26

11.5.1.3.3 Statistical considerations

As a result of the interim analysis, the two-sided significance level for testing treatment differences was set at 0.047. Please refer to section 11.3.1.3.3, page 29, for the remainder of the statistical analysis.

11.5.1.4 Results

11.5.1.4.1 Populations enrolled/analyzed

The Intent-to-treat (ITT) and Safety populations consisted of all randomized subjects who received study medication. The results for the primary efficacy and select secondary variables were also presented for the PP population. The Per Protocol (PP) population included all subjects who did not violate the protocol in ways that would effect efficacy evaluations for the double-blind phase. There were 186 subjects randomized (ASM 1%=123, vehicle=63) to treatment during the 6-week, double-blind treatment phase of the study on 5 continents. A total of 173 subjects subsequently entered the 20-week open-label phase. Subject disposition is shown in table 30.

Table 30
Subject Disposition – Study B316

Number of subjects	ASM 1%/ASM 1% N (%)	Vehicle/ASM 1% N (%)	Total N (%)
Screened	n/a	n/a	211
Randomized	123	63	186
Treated †	123 (100.0)	63 (100.0)	186 (100.0)
Completed DB phase †	109 (88.6)	33 (52.4)	142 (76.3)
Entered OL phase †	117 (95.1)	56 (88.9)	173 (93.0)
Completed OL phase ‡	94 (80.3)	48 (85.7)	142 (82.1)

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

† Denominator for percentages is the number of randomized subjects
‡ Denominator for percentages is the number of subjects entering the open-label phase
n/a = not applicable, DB = double-blind, OL = open-label

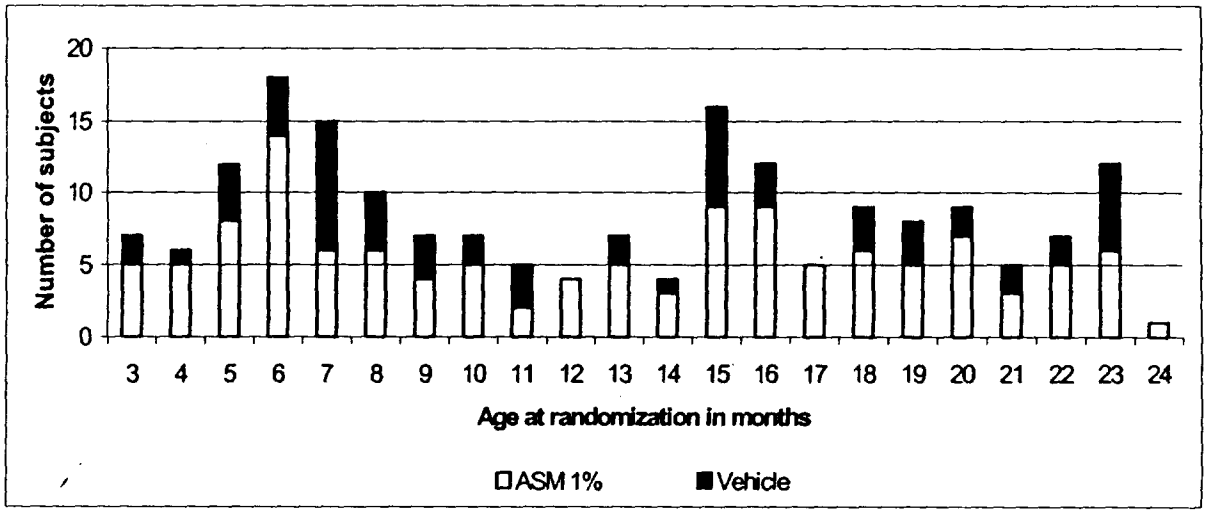
Subjects' baseline demographics are detailed in table 31 and figure 3 shows a schematic representation of patient ages.

Table 31
Baseline Demographics – ITT Population
Study B316

Parameter		ASM 1% (N=123)	Vehicle (N=63)	p-values
Age (months)	mean ± SD	12.6 ± 6.25	12.7 ± 6.29	0.891 †
	range	3 - 24	3 – 23	
Sex (n, %)	Male	68 (55.3)	34 (54.0)	0.878 ‡
	Female	55 (44.7)	29 (46.0)	
Race (n, %)	Caucasian	65 (52.8)	44 (69.8)	0.153 ‡
	Black	16 (13.0)	4 (6.3)	
	Oriental	3 (2.4)	1 (1.6)	
	Other	39 (31.7)	14 (22.2)	
Height (cm)	mean ± SD	74.7 ± 7.54	75.0 ± 8.52	0.225 *
	range	59 - 92	60 – 98	
Weight (kg)	mean ± SD	9.5 ± 1.94	9.8 ± 1.84	0.063 *
	range	6 - 15	6 – 14	

Source: Post-text tables 7.4-1, 10.4-3
† Wilcoxon Rank Sum Test
‡ Fishers Exact Test
* Van Elteren Test, stratified by age category

Figure 3
Age distribution at randomization – B316



Source: Post text table 7.4-8

Reviewer's Comment: *There were 91 infants out of the 186 patients that were ≤ 12 months of age (49%). Of these 91 subjects, 59 (65%) were in the ASM cream 1% arm. The age*

distribution at randomization shows that an adequate number of infants were in the first year of life and on study drug to make an efficacy assessment of this age group valid for age.

Reasons for discontinuation in the double-blind phase and in the open-label phase are described in tables 32 and 33, respectively.

Table 32
Subject Discontinuations – Double-blind Phase
ITT Population – Study B316

	ASM 1% (N=123)		Vehicle (N=63)		Total (N=186)	
	N	(%)	N	(%)	N	(%)
Completed	109	(88.6)	33	(52.4)	142	(76.3)
All discontinuations	14	(11.4)	30	(47.6)	44	(23.7)
Reasons for discontinuation						
Unsatisfactory therapeutic effect	8	(6.5)	26	(41.3)	34	(18.3)
Protocol violation	2	(1.6)	1	(1.6)	3	(1.6)
Withdrawal of consent	2	(1.6)	2	(3.2)	4	(2.2)
Lost to follow up	2	(1.6)	1	(1.6)	3	(1.6)

* Subjects who discontinued the study for unsatisfactory therapeutic effect after ≥3 weeks double-blind treatment were allowed to enter the open-label treatment phase.
Source: Post-text table 7.1-3

Table 33
Subjects Discontinued from Open-label Phase
ITT Population – Study B316

	ASM 1%/ASM 1% (N=117)		Vehicle/ASM 1% (N=56)		Total (N=173)	
	N	(%)	N	(%)	N	(%)
Completed	94	(80.3)	48	(85.7)	142	(82.1)
All discontinuations	23	(19.7)	8	(14.2)	31	(17.9)
Reason for discontinuation						
Adverse event	4	(3.5)	1	(1.8)	5	(2.9)
Unsatisfactory therapeutic effect	15	(12.9)	5	(9.0)	20	(11.5)
Protocol violation	3	(2.6)	3	(1.8)	4	(2.3)
Lost to follow-up	1	(0.9)	0	(1.8)	2	(1.2)

Source: Post-text table 7.1-4

Table 34 shows the percentage of subjects with major protocol violations during the double-blind phase of the study. The overall protocol violation rate was higher in the vehicle-treated group and can be attributed to the use of prohibited medications for the treatment of atopic dermatitis. These protocol violations accounted for only 3 terminations during the double-

blind phase, and subjects with significant protocol violations were excluded from the double-blind phase Per Protocol analysis population.

Table 34
Major Protocol Violations – Double-Blind Phase
ITT Population – Study B316

Protocol violation	ASM 1% (N=123) N (%)	Vehicle (N=63) N (%)	Total (N=186) N (%)
Subjects with any protocol violation	28 (22.8)	22 (34.9)	50 (26.9)
Under-compliant: Missed >10% of doses	13 (10.6)	8 (12.7)	21 (11.3)
<5% BSA involvement at baseline	10 (8.0)	4 (6.4)	14 (7.5)
Treated with: Antihistamine	6 (4.9)	7 (11.1)	13 (7.0)
Anti-pruritic for AD without stable Baseline dose	9 (7.3)	4 (6.3)	13 (7.0)
Topical steroids †	3 (2.4)	7 (11.1)	10 (5.4)
Systemic steroids †	2 (1.6)	2 (3.2)	4 (2.2)
Missed >2 scheduled visits or no post-Baseline assessments	1 (0.8)	0	1 (0.5)

† Used ≤1 week (topicals) or ≤1 month (systemics) of Baseline or during double-blind phase of study.
Note: Subjects with more than one major protocol violation were counted in each category
No subjects excluded for (a) Baseline IGA score <2 or >3, or (b) leukotriene antagonist used within 1 week of Baseline.
Source: Post-text table 7.1-9

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

Table 35
Baseline Disease Characteristics
ITT Population – B316

Parameter	Parameter	ASM 1% (N=123)	Vehicle (N=63)	p-value
IGA score (n, %)	2 (mild)	40 (32.5)	21 (33.3)	0.911
	3 (moderate)	83 (67.5)	42 (66.7)	
%TBSA Distribution (n, %)	≤ 5%	15 (12.2)	4 (6.3)	0.135
	>5% - ≤15%	25 (20.3)	26 (41.3)	
	>15% - ≤30%	38 (30.9)	16 (25.4)	
	>30% - ≤60%	34 (27.6)	12 (19.0)	
	>60%	11 (8.9)	5 (7.9)	
% TBSA involved	mean ± SD	27.4 ± 20.79	23.0 ± 18.63	n/a
	range			

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

Reviewer's Comment: *There were 91 infants ≤ 12 months of age and 95 infants > 12 months of age. Fifty-three of the 91 (58%) infants in the first year of life had a TBSA of ≥ 15%. Of those 53 patients, 38 (72%) were in the ASM 1% cream arm. For the infants >12 months of age, 65 of the 95 subjects (68%) had a TBSA of ≥ 15%. Of those 65 subjects, 46 (71%) were on ASM 1% cream. Thus, there was an adequate representation of infants in the study in both groups that had at least moderate disease at baseline.*

Table 36 shows the number of days that patients were exposed to the study medication or vehicle in both the double-blind and open-label phases of the study.

Table 36
Total Exposure to Study Medication
ITT Population – B316

	ASM 1%/ASM 1%		Vehicle/ASM 1%	
	N	Mean ± SD	N	Mean ± SD
Double-blind				
Drug Days	123	36.5 ± 10.0	63	30.5 ± 12.1
Treatment Days	123	37.2 ± 9.8	63	31.0 ± 12.1
Open-label				
Drug Days	117	97.6 ± 47.7	56	85.0 ± 49.6
Treatment Days	117	101.7 ± 45.8	56	90.6 ± 50.0
Both phases †				
Drug Days	123	128.6 ±57.5	56	85.0 ±49.6
Treatment Days	123	133.2 ±56.4	56	90.6 ± 49.0

† Total exposure to ASM 1% during both phases
Drug day was defined as: 1 day for bid 0.5 days for od 0 for drug not taken
Treatment days were defined as: 1 day for bid or od 0 for drug not taken
Source: Post-text table 8.1-13 , 8.1-15

11.5.1.4.2 Efficacy endpoint outcomes

Treatment success was defined as an Investigator's Global Assessment of clear (0) or almost clear (1), in the intent-to-treat population. Table 37 shows the results of the investigator's global assessment.

Table 37
Treatment Success – IGA Double-blind Phase
ITT Population – Study B316

	ASM 1% (N=123)		Vehicle (N=63)		p-value †
	N	(%)	N	(%)	
Baseline	0		0		
Day 8	21	(17.1)	6	(9.5)	0.174
Day 15	46	(37.4)	10	(15.9)	<0.001
Day 22	54	(43.9)	11	(17.5)	<0.001
Day 29	65	(52.8)	11	(17.5)	<0.001
Day 43	67	(54.5)	15	(23.8)	<0.001

† Derived from Cochran-Mantel-Haenszel test, stratified by center
Note: Treatment success is defined as an IGA score of 0 (clear) or 1 (almost clear)
Source: Post-text table 9.1-1

ASM 1% cream was statistically significantly superior to vehicle at the efficacy time point (day 43). It was also statistically significantly superior to vehicle starting at day 15 and this was maintained until the end of the study.

Table 38 shows the frequency distribution of IGA at each visit. There was a statistically significant difference between the treatment groups in the distribution of IGA scores at all post-Baseline assessments from Day 8 to Endpoint. At Endpoint, a greater proportion of the ASM 1% treated subjects achieved treatment success with IGA scores ≤1 (54.5%). Only 23.8% of the subjects treated with vehicle had comparable IGA scores.

Table 38
Frequency Distribution of IGA By Visit
ITT Population – B316

Visit		IGA score						
Group	N	0	1	2	3	4	5	p-value †
Baseline								
ASM 1%	123	0	0	40 (32.5)	83 (67.5)	0	0	-
Vehicle	63	0	0	21 (33.3)	42 (66.7)	0	0	
Day 8								
ASM 1%	123	3 (2.4)	18 (14.6)	68 (55.3)	34 (27.6)	0	0	<0.001
Vehicle	63	0	6 (9.5)	21 (33.3)	33 (52.4)	3 (4.8)	0	
Day 15								
ASM 1%	123	3 (2.4)	43 (35.0)	44 (35.8)	33 (26.8)	0	0	<0.001
Vehicle	63	0	10 (15.9)	18 (28.6)	33 (52.4)	2 (3.2)	0	
Day 22								
ASM 1%	123	6 (4.9)	48 (39.0)	38 (30.9)	30 (24.4)	1 (0.8)	0	<0.001
Vehicle	63	1 (1.6)	10 (15.9)	18 (28.6)	30 (47.6)	3 (4.8)	1 (1.6)	
Day 29								
ASM 1%	123	15 (12.2)	50 (40.7)	30 (24.4)	25 (20.3)	2 (1.6)	1 (0.8)	<0.001
Vehicle	63	3 (4.8)	8 (12.7)	16 (25.4)	29 (46.0)	6 (9.5)	1 (1.6)	
Day 43								
ASM 1%	123	24 (19.5)	43 (35.0)	28 (22.8)	24 (19.5)	3 (2.4)	1 (0.8)	<0.001
Vehicle	63	3 (4.8)	12 (19.0)	12 (19.0)	30 (47.6)	5 (7.9)	1 (1.6)	

Source: Post-text table 9.1-2

† Cochran-Mantel-Haenszel row mean score test, stratified by center

Treatment success: 0=Clear, 1=Almost Clear
Treatment failure: 2=Mild, 3=Moderate, 4=Severe 5=Very Severe

There was a statistically significant difference between the treatment groups in the distribution of IGA scores at all post-Baseline assessments from Day 8 to Endpoint. At Endpoint, a greater proportion of the ASM 1% treated subjects achieved treatment success with IGA scores ≤1 (54.5%). Only 23.8% of the subjects treated with vehicle had comparable IGA scores.

Table 39 shows the treatment success by baseline IGA and by baseline % TBSA involved during the double-blind phase of the study.

Table 39
Treatment success[†] by Baseline IGA and by Baseline %TBSA Involved
Double-blind Phase – ITT population – Study B316

	ASM 1% (N=123)		Vehicle (N=63)		p-value [‡]
	N[#]	N (%)	N[#]	N (%)	
Baseline IGA					
Overall	123	67 (54.5)	63	15 (23.8)	<0.001
2	40	26 (65.0)	21	10 (47.6)	
3	83	41 (49.4)	42	5 (11.9)	
Baseline %TBSA involved					
Overall	123	67 (54.5)	63	15 (23.8)	<0.001
≤ 5%	15	7 (46.7)	4	0	
> 5 % - ≤ 15%	25	20 (80.0)	26	8 (30.8)	
> 15% - ≤ 30%	38	21 (55.3)	16	2 (12.5)	
> 30% - ≤60%	34	17 (50.0)	12	5 (41.7)	
> 60%	11	2 (18.2)	5	0	

[†] Defined as a score of 0 or 1
[‡] Derived from CMH test stratified by Baseline factor
[#] Number of subjects assessed
Source: Post-text tables 9.1-5 and 9.1-6

When analyzed against Baseline IGA, the majority of subjects overall achieved treatment success when treated with ASM 1%. The greatest difference in the proportions of subjects with treatment success at Endpoint was seen in subjects with moderate Baseline disease (ASM 1% = 49.4%, vehicle = 11.9%). The treatment success rate across the Baseline %TBSA categories was fairly consistent at 45-55%, although a response rate of 80.0% was seen in subjects with between 5-15% TBSA involved.

The majority of subjects (70%) on ASM 1% with moderate Baseline disease had improved by Endpoint and approximately 5% subjects had a worsening of their condition. In contrast, 64% of subjects on vehicle with moderate Baseline disease remained unchanged or worsened at Endpoint. Similarly, the majority of subjects on ASM 1% with mild disease at Baseline had improved and only 7.5% subjects worsened at Endpoint. In contrast, 42.9% of subjects on vehicle with mild disease at Baseline had worsened at Endpoint.

Reviewer's Comment: *At endpoint, ASM 1% cream showed its most significant effect in the moderate disease category and in TBSA involvement of 5-15%. This does support the proposed indication of mild to moderate disease activity. Further, only a small percentage of patients on ASM 1% cream had a worsening of their disease when compared with vehicle.*

The secondary efficacy parameters were the key signs of atopic dermatitis: erythema, infiltration/papulation, excoriation and lichenification and the symptom of pruritus. Table 40 shows the proportion of patients with absent or mild signs at endpoint as compared to baseline and vehicle.

Table 40
Number (%) of Subjects with Mild or Absent Key Signs of AD
ITT Population – B316

Visit	Treatment group		Erythema		Infiltration/ papulation		Excoriation		Lichenification	
		N	N	(%)	N	(%)	N	(%)	N	(%)
Double-blind phase										
Baseline	ASM 1%	123	26	(21.1)	31	(25.2)	67	(54.5)	84	(68.3)
	Vehicle	63	13	(20.6)	20	(31.7)	40	(63.5)	44	(69.8)
Day 15	ASM 1%	123	82	(66.7)	86	(69.9)	105	(85.4)	94	(76.4)
	Vehicle	63	17	(27.0)	27	(42.9)	41	(65.1)	47	(74.6)
Day 22	ASM 1%	123	82	(66.7)	86	(69.9)	102	(82.9)	97	(78.9)
	Vehicle	63	26	(41.3)	26	(41.3)	40	(63.5)	41	(65.1)
Endpoint	ASM 1%	123	88	(71.5)	86	(69.9)	101	(82.1)	99	(80.5)
	Vehicle	63	19	(30.2)	24	(38.1)	37	(58.7)	41	(65.1)
Open-label phase										
Baseline[†]	ASM 1% / ASM 1%	117	85	(72.6)	83	(70.9)	96	(82.1)	94	(80.3)
	Vehicle / ASM 1%	56	17	(30.4)	21	(37.5)	31	(55.4)	36	(64.3)
Endpoint	ASM 1% / ASM 1%	117	80	(68.4)	78	(66.7)	95	(81.2)	92	(78.6)
	Vehicle / ASM 1%	56	37	(66.1)	37	(66.1)	43	(76.8)	48	(85.7)

All body regions for the given sign with a score of 1 or less (mild or absent signs)
[†] Last double-blind assessment prior to entry into open-label phase
Source: Post-text table 9.2-15, 9.2-28

Table 41 shows the pruritus assessment at baseline, day 8 and day 43. At baseline, there was not a significant difference between arms in the severity of pruritus. Beginning at day 8, there was a statistically significant difference between ASM 1% cream and vehicle in patients who had either no pruritus or mild pruritus.

Table 41
Frequency of Pruritus Assessment
ITT Population – Study B316

		N	0 Absent N (%)	1 Mild N (%)	2 Moderate N (%)	3 Severe N (%)	p-value † Score = 0	p-value † Score = 0, 1
Double-blind phase								
Baseline	ASM 1%	123	6 (4.9)	29 (23.6)	45 (36.6)	43 (35.0)	0.596	0.896
	Vehicle	63	2 (3.2)	16 (25.4)	24 (38.1)	21 (33.3)		
Day 8	ASM 1%	123	23 (18.7)	63 (51.2)	24 (19.5)	13 (10.6)	0.014	<0.001
	Vehicle	63	4 (6.3)	19 (30.2)	17 (27.0)	23 (36.5)		
Day 43	ASM 1%	123	55 (44.7)	34 (27.6)	20 (16.3)	14 (11.4)	<0.001	<0.001
	Vehicle	63	6 (9.5)	15 (23.8)	16 (25.4)	26 (41.3)		
Open-label phase								
Baseline*	ASM 1%/ASM 1%	117	54 (46.2)	31 (26.5)	20 (17.1)	12 (10.3)	n/a	n/a
	Vehicle/ASM 1%	56	5 (8.9)	13 (23.2)	16 (28.6)	22 (39.3)		
Week 27	ASM 1%/ASM 1%	117	48 (41.0)	31 (26.5)	13 (11.1)	25 (21.4)	n/a	n/a
	Vehicle/ASM 1%	56	20 (35.7)	18 (32.1)	10 (17.9)	8 (14.3)		

† CMH general association test adjusted for center
* Baseline for the open-label is last double-blind assessment prior to entry into the open-label phase
n/a = not applicable
Source: Post-text table 9.2-29 , 9.2-30 , 9.2-31 9.2-32

Reviewer's Comment: *Statistical significance was reached by day 8 for patients on ASM 1% cream who had absent and/or mild pruritus. This was maintained throughout the remainder of the double-blind portion of the study. Although statistical analysis was not preformed for the open-label portion of the study, it can be seen from table 39 that the percentage of patients who had an absence of pruritus by week 27 that were switched from vehicle to ASM 1% cream approached the percentage of those who had always been on ASM 1% cream.*

11.5.1.4.3 Conclusions Regarding Efficacy Data

Study B316 supports the claim that SDZ ASM 981 1% cream is superior to vehicle in the treatment of atopic dermatitis [redacted] who had mild to moderate disease by reaching statistical significance at endpoint, day 43 ($p<0.001$) in the Investigator's Global Assessment]. This statistical significance began at day 15 ($p<0.001$) and was maintained throughout the remainder of the study. The secondary endpoints support this conclusion.

11.5.1.5 Safety outcomes

The safety population included all patients who were randomized and received at least one dose of study medication (the ITT population). There were 186 patients in the safety population, 123 on ASM 1% cream and 63 on vehicle. Safety outcomes are in two phases, the 6-week double-blind phase and the 20-week open label phase.

Reviewer's Comment: *Although there was a high number of discontinuations in the vehicle group (30 out of 60 subjects), since 56 subjects entered the open-label phase, 23 of the 26 subjects (88%) did have at least 3 weeks of treatment on vehicle before they entered the open-label phase of the study. This was a protocol requirement if the discontinuation was for unsatisfactory therapeutic effect. Thus, in this reviewer's opinion, enough patients on vehicle were in the study long enough to make a direct comparison of adverse events between ASM cream 1% and vehicle.*

Tables 42 and 43 are an overall summary of treatment-emergent adverse events for the infant population ages 3 months – 23 months of age.

Table 42
Overall Summary of Treatment-Emergent Adverse Events
Study B316 Double-Blind Phase – Safety Population

	ASM 1% (N=123)		Vehicle (N=63)		P-value
	N	(%)	N	(%)	
At least 1 AE	97	(78.9)	41	(65.1)	**0.052**
At least 1 local AE	27	(22.0)	18	(26.6)	0.367
Any drug related AE†	7	(5.7)	8	(12.7)	0.152

† Adverse events considered by the investigator to be 'suspected' as related to study medication.
Source: Post-text table 10.1-1

Table 43
Overall Summary of Treatment-Emergent Adverse Events
Study B316 – Open Label Phase – Safety Population

	ASM 1%/ASM 1% (N=117)		Vehicle/ASM 1% (N=56)	
	N	(%)	N	(%)
At least 1 AE	93	(79.5)	44	(78.6)
At least 1 local AE	28	(23.9)	16	(28.6)
Any drug related AE†	3	(2.6)	5	(8.9)

† Adverse events considered by the investigator to be 'suspected' as related to study medication.
Source: Post-text table 10.1-1

Reviewer's Comment: *The number of infants with adverse events on ASM 1% cream in the double-blind phase of the study approaches statistical significance (p=0.052). This significance has to reflect the incidence of systemic AEs as there was not a significance found between infants on ASM cream 1% and vehicle for locally (cutaneous) occurring adverse events. The important piece of information to be gleaned from the open-label phase is that while infants who continued on ASM 1% cream remain fairly constant in their incidence rate of adverse events (79.5%) the infants who are switched from vehicle to ASM 1% cream show a rise in adverse events ((from*

65.1% to 78.6%). The final result is comparable with those that had been on ASM 1% cream the entire study (79.5% vs. 78.6%).

Table 44 shows the incidence of adverse events by class system for any event that occurred in 1% of the infant population or greater.

Table 44
Incidence rates of common (≥ 1% in any treatment group) treatment emergent adverse Events - Study B316 – Double-Blind Phase (Safety population)

	ASM 1% (N=123) N (%)	Vehicle (N=63) N (%)	Treatment difference & 95% Confidence Interval or p value*
At least 1 AE	97 (78.9%)	41 (65.1%)	13.8% 0.052
At least 1 common AE	84 (68.3%)	39 (61.9%)	9.7% (-4.3%, 23.8%)
Infections and infestations			
Total	67 (54.5%)	27 (42.9%)	
Upper respiratory tract Infection NOS	29 (23.6%)	9 (14.3%)	9.3% (-2.2%, 20.7%)
Nasopharyngitis	18 (14.6%)	5 (7.9%)	6.7% (-2.4%, 15.8%)
Gastroenteritis NOS	9 (7.3%)	2 (3.2%)	4.1% (-2.2%, 10.5%)
Bronchitis NOS	7 (5.7%)	3 (4.8%)	
Influenza	7 (5.7%)	2 (3.2%)	2.5% (-3.4%, 8.5%)
Otitis media NOS	5 (4.1%)	0	4.1% (0.6%, 7.6%)
Bacterial infection NOS	1 (0.8%)	4 (6.3%)	-5.5% (11.8%, 0.7%)
Pharyngitis NOS	2 (1.6%)	2 (3.2%)	
Stye	2 (1.6%)	0	
Tinea NOS	2 (1.6%)	0	
Upper Respiratory Tract Infection Viral NOS	2 (1.6%)	0	
Sinusitus NOS	1 (0.8%)	1(1.6%)	
Scabies infestation	0	2 (3.2%)	-3.2% (-7.5%, 1.2%)
Bronchopheumonia NOS	0	1(1.6%)	
Eye Infection Bacterial NOS	0	1(1.6%)	
Folliculitis	0	1(1.6%)	
Otitis Media Serous NOS	0	1(1.6%)	
Respiratory Tract Infection NOS	0	1(1.6%)	
Rubella	0	1 (1.6%)	
Skin Infection NOS	0	1 (1.6%)	
Tonsillitis NOS	0	1 (1.6%)	
General disorders and administration site conditions			
Total	47 (38.2%)	14 (22.2%)	
Pyrexia	39 (31.7%)	8 (12.7%)	19% (7.4%, 30.6%)
Application site irritation	0	3(4.8%)	-4.8% (-10.0%, 0.5%)
Application Site Reaction NOS	2 (1.6%)	1(1.6%)	
Application Site Burning	1(0.8%)	1(1.6%)	
Application Site Erythema	2 (1.6%)	0	
Pain NOS	2 (1.6%)	0	
Influenza Like Illness	0	1 (1.6%)	
Respiratory, thoracic and mediastinal disorders			
Total	23 (18.7%)	15 (25.4%)	
Rhinitis NOS	6 (4.9%)	5 (7.9%)	-3.1% (-10.7%, 4.6%)
Asthma NOS	7 (5.7%)	2 (3.2%)	2.5% (-3.4%, 8.5%)
Cough	5 (4.1%)	3 (4.8%)	
Bronchospasm NOS	4 (3.3%)	3 (4.8%)	
Nasal congestion	3 (2.4%)	3 (4.8%)	-2.3% (-8.2%, 3.6%)
Rhinorrhea	4 (3.3%)	1 (1.6%)	

	ASM 1% (N=123) N (%)	Vehicle (N=63) N (%)	Treatment difference & 95% Confidence Interval or p value*
Chest Tightness	2 (1.6%)	0	
Wheezing	2 (1.6%)	0	
Asthma Aggravated	0	1 (1.6%)	
Gastrointestinal disorders			
Total	28 (22.8%)	7 (11.1%)	
Teething	10 (8.1%)	3 (4.8%)	3.4% (-3.8%, 10.5%)
Diarrhea NOS	10 (8.1%)	0	8.1% (3.3%, 13.0%)
Vomiting NOS	5 (4.1%)	3 (4.8%)	
Gingival Pain	2 (1.6%)	0	
Loose Stools	2 (1.6%)	0	
Nausea	2 (1.6%)	0	
Abdominal pain Upper	0	1 (1.6%)	
Psychiatric disorders			
Total	12 (9.8%)	6 (9.5%)	
Restlessness	10 (8.1%)	3 (4.8%)	3.4% (-3.8, 10.5%)
Irritability	1 (0.8%)	2 (3.2%)	-2.4% (-7.0%, 2.2%)
Sleep Disorder NOS	2 (1.6%)	1 (1.6%)	
Blood and lymphatic system disorders			
Total	6 (4.9%)	3 (4.8%)	
Anemia NOS	2 (1.6)	2 (3.2)	
Iron deficiency anemia	3 (2.4)	0	2.4% (-0.3%, 5.2%)
Lymphandenopathy	1 (0.8%)	1 (1.6%)	
Skin & subcutaneous tissue Disorders			
Total	12 (9.8%)	6 (9.5%)	
Dermatitis contact	4 (3.3%)	1 (1.6%)	
Pruritus	1 (0.8%)	1 (1.6%)	
Urticaria	1 (0.8%)	1 (1.6%)	
Eyelid edema	0	1 (1.6%)	
Rash Papular	0	1 (1.6%)	
Skin Ulcer NOS	0	1 (1.6%)	
Eye disorders			
Total	4 (3.3%)	2 (3.2%)	
Conjunctivitis NEC	2 (1.6%)	2 (3.2%)	
Immune System Disorders			
Total	4 (3.3%)	2 (3.2%)	
Food Allergy	2 (1.6%)	0	
Hypersensitivity	1 (0.8%)	1 (1.6%)	
Injury and poisoning			
Total	8 (6.5%)	2 (3.2%)	
Abrasion NOS	4 (3.3%)	0	
Limb Injury NOS	2 (1.6%)	0	
Head Injury	0	1 (1.6%)	
Laceration	0	1 (1.6%)	
Nervous system disorders			
Total	1 (0.8%)	2 (3.2%)	
Insomnia NEC	1 (0.8%)	2 (3.2%)	-2.4% (-7.0%, 2.2%)

Source: Post-text table 10.1-1, 10.1-2b, Volume 5-50

*listed for those occurring with ≥2.0 % treatment difference

Reviewer's Comment: *Table 44 shows that several adverse events occurred in the ASM 1% cream arm that were statistically significant as compared to vehicle. These were pyrexia (31.7% vs. 12.7%), diarrhea (8.1 % vs. 0%), and otitis media (4.1% vs. 0%). Although not statistically*

significant, there was a clinically significant treatment difference in several other adverse events in events treated with ASM 1% cream as compared to those on vehicle. These were upper respiratory tract infection (treatment difference 9.3%), nasopharyngitis (6.7%), gastroenteritis (4.1%), teething (3.4%), restlessness (3.4%), asthma (2.5%) and iron deficiency anemia (2.4%).

Although iron deficiency anemia was listed as an adverse event in the table, further review of the data which follows suggest that this should not be listed as an adverse event. There were 3 cases reported as iron deficiency anemia. On review of the case report forms, only 2 of the cases had documented anemia. Both subjects, subject 0701-0001, a 13 month old from South Africa, and subject 0701-0006, a 22 month old from South Africa, had abnormal hemoglobin/hematocrit values at baseline. No further workup of the anemia was documented (i.e., MCV, MCH, Fe, TIBC). It was documented that the mother of the former subject had been anemic throughout her pregnancy. Both subjects remained anemic at the end of the study, although the subject 0701-0001 had improved and the other subject was not appreciably worse. The third subject, 0708-00011, on review of the case report form had normal hemoglobin and hematocrit values throughout the study. Therefore, it is not clear why this subject was labeled as having anemia.

The evidence of the data here shows that anemia in this population was not a treatment emergent adverse event and most likely due to inadequate nutrition. As such, these incidences should not be included in the adverse event table. Although limb injury and poisoning occurred during the study, there is not any preclinical evidence that this might be a direct effect of ASM 1% cream (i.e. there was not evidence of ataxia in animals).

The majority of the adverse events listed in table 44 were rated as mild to moderate by the investigators. There were only a few cases of adverse events that were rated as severe but the majority of those cases occurred in the ASM 1% cream arm and included one case each of nasopharyngitis, asthma, application site erythema, restlessness, flushing, appetite decrease, and pruritus.

The open-label phase supports the poor safety profile in infants of ASM 1% cream, as in most cases, infants who were on ASM 1% cream in the open-label phase who had been on vehicle in the double-blind phase began to experience the same, if not higher rate of occurrence of these same adverse events as those who had been on ASM 1% cream in the double-blind phase. Table 45 delineates these convergent adverse events.

Table 45
Incidence Rates of Convergent Treatment Emergent Adverse Events - Study B316 – Open-Label Phase (Safety population)

	ASM 1%/ASM 1% (N=117) N (%)	Vehicle/ASM 1% (N=56) N (%)	Treatment difference & 95% Confidence Interval or p value
At least 1 common AE	91 (77.8%)	44 (78.6%)	
Infections and infestations			
Upper respiratory tract Infection NOS	25 (21.4%)	12 (21.4%)	-0.1% (-13.1%, 13.0%)
Nasopharyngitis	16 (13.7%)	12 (21.4%)	-7.8% (-20.2%, 4.7%)
Otitis Media NOS	11 (9.4%)	4 (7.1%)	2.3% (-6.3%, 10.8%)
Gastroenteritis NOS	7 (6.0%)	5 (8.9%)	-2.9% (-11.6%, 5.7%)
Upper Respiratory Tract Infection Viral NOS	3 (2.6%)	3 (5.4%)	-2.8% (-9.3%, 3.8%)
General disorders and administration site conditions			
Pyrexia	32 (27.4%)	15 (26.8%)	0.6 (-13.6%, 14.7%)
Gastrointestinal disorders			
Teething	12 (10.3%)	5 (8.9%)	1.3% (-7.9%, 10.6%)
Diarrhea NOS	10 (8.5%)	3 (5.4%)	3.2% (-4.6%, 11.0%)
Psychiatric disorders			
Restlessness	10 (8.5%)	4 (7.1%)	1.4% (-7.0%, 9.8%)

Source: Adapted from post-text table 10.1-12a, Volume 5-50

As can be seen from table 45, the incidence of these adverse events, nasopharyngitis, URIs, pyrexia etc., remained fairly constant for infants who continued on ASM 1% cream, but for those who switched to ASM 1% cream from vehicle, the incidence of these events approached if not surpassed the incidence in the ASM 1% cream arm. The incidence of otitis media illustrates the convergence. The incidence of this infection rose from 0% in the vehicle arm in the double-blind phase to 7.1% after infants were treated with ASM 1% cream in the open-label phase. The incidence also rose in the ASM 1% cream arm from 4.1% to 9.4%, suggesting, also that risk increases with duration of exposure to the drug (6 weeks vs. 26 weeks). This data suggests that there is a clear correlation between the increase in these adverse events and the use of ASM 1% cream in infants.

Table 46 delineates the common treatment emergent adverse events that occurred in ≥ 1% of the population in the open-label phase, where all patients are now on ASM 1% cream, that has not already been addressed in table 45.

Table 46
Incidence Rates of Common (≥ 1% in any treatment group) Emergent Adverse Events*
B316 – Open Label Phase (Safety Population)

	ASM 1%/ASM 1% (N=117) N (%)	Vehicle/ ASM 1% (N=56) N (%)	Treatment difference & 95% Confidence Interval or p value
At least 1 common AE	91 (77.8%)	44 (78.6%)	-0.8% (-13.9%, 12.3%)
Infections and infestations			
Bronchitis NOS	11 (9.4%)	5 (8.9%)	0.5% (-8.7%, 9.6%)
Tonsillitis	6 (5.1%)	3 (5.4%)	-0.2% (-7.4%, 6.9%)
Bacterial Infection NOS	4 (3.4%)	2 (3.6%)	-0.2% (-6.0%, 5.7%)
Ear Infection NOS	5 (4.3%)	0	4.3% (0.6%, 7.9%)
Molluscum Contagiosum	5 (4.3%)	0	4.3% (0.6%, 7.9%)
Chickenpox	3 (2.6%)	1 (1.8%)	0.8% (-3.7%, 5.3%)
Bronchitis Acute NOS	1 (0.9%)	2 (3.6%)	-2.7% (-7.9%, 2.4%)
Croup Infectious	0	3 (5.4%)	-5.4% (-11.3%, 0.5%)
Influenza	3 (2.6%)	0	2.6% (-0.3%, 5.4%)
Pneumonia NOS	3 (2.6%)	0	2.6% (-0.3%, 5.4%)
Sinusitis NOS	3 (2.6%)	0	2.6% (-0.3%, 5.4%)
Skin Infection NOS	1 (0.9%)	2 (3.6%)	-2.7% (-7.9%, 2.4%)
Gastrointestinal Infection NOS	2 (1.7%)	0	1.7% (0.6%, 4.1%)
Mumps	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Pharyngitis NOS	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Viral Infection NOS	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Folliculitis	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Hand, Foot, and Mouth Disease	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Hepatitis B	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Herpes Simplex Dermatitis	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Otitis Media Serous NOS	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Pharyngitis Streptococcal	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Tinea Capitis	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Tonsillitis Acute NOS	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
General disorders and administration site conditions			
Influenza Like Illness	1 (0.9%)	2 (3.6%)	-2.7% (-13.6%, 14.7%)
Injection Site Pain	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Application Site Burning	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Respiratory, thoracic and mediastinal disorders			
Cough	11 (9.4%)	3 (5.4%)	4.0% (-3.9%, 12.0%)
Rhinitis NOS	6 (5.1%)	7 (12.5%)	-7.4% (-16.9%, 2.2%)
Bronchospasm NOS	3 (2.6%)	1 (1.8%)	0.8% (-3.7%, 5.3%)
Asthma NOS	2 (1.7%)	1 (1.8%)	-0.1% (-4.3%, 4.1%)
Nasal congestion	2 (1.7%)	1 (1.8%)	-0.1% (-4.3%, 4.1%)
Rhinorrhea	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Asthma Aggravated	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Gastrointestinal disorders			
Vomiting NOS	3 (2.6%)	1 (1.8%)	0.8% (-3.7%, 5.3%)
Sore Throat NOS	1 (0.9%)	2 (3.6%)	-2.7% (-7.9%, 2.4%)
Abdominal pain Upper	0	2 (3.6%)	-3.6% (-8.4%, 1.3%)
Gingival Pain	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Constipation	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Toothache	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Blood and lymphatic system disorders			
Anemia NOS	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Skin & subcutaneous tissue Disorders			

	ASM 1%/ASM 1% (N=117) N (%)	Vehicle/ ASM 1% (N=56) N (%)	Treatment difference & 95% Confidence Interval or p value
Dermatitis contact	3 (2.6%)	4 (7.1%)	-4.6% (-11.9%, 2.7%)
Erythema	3 (2.6%)	0	2.6% (-0.3%, 5.4%)
Skin Lesion NOS	3 (2.6%)	0	2.6% (-0.3%, 5.4%)
Dermatitis NOS	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Heat Rash	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Urticaria NOS	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Intertrigo	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Eye disorders			
Conjunctivitis NEC	4 (3.4%)	2 (3.6%)	-0.2% (-6.0%, %.7%)
Immune System Disorders			
Hypersensitivity	4 (3.4%)	1 (1.8%)	1.6% (-3.1%, 6.4%)
Food Allergy	2 (1.7%)	3 (3.6%)	-1.9% (-7.3%, 3.5%)
Injury and poisoning			
Animal Bite	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Animal Scratch	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Sunburn	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Nervous system disorders			
Headache NOS	2 (1.7%)	0	1.7% (-0.6%, 4.1%)
Insomnia NEC	1 (0.9%)	1 (1.8%)	-0.9% (-4.8%, 2.9%)
Ear and Labyrinth Disorders			
Earache	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Hepato-biliary Disorders			
Cholestasis	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)
Metabolism and Nutrition Disorders			
Failure to Thrive	0	1 (1.8%)	-1.8% (-5.3%, 1.7%)

Source: Post-text table 10.1-12a, Volume 5-50 * Events not already addressed in table 43.

Reviewer's Comment: *There are a couple of key points to be ascertained from this table. First, there are a few newly emergent adverse events in this open-label phase (20 weeks) that were not listed in the double-blind (6 week) phase for infants who had been on ASM 1% cream for 26 weeks. Those that have not been mentioned above in table 43 include ear infection NOS (4.3%), molluscum contagiosum (4.3%), tonsillitis (5.1%), skin erythema (2.6%), skin lesion NOS (2.6%), chickenpox (2.6%), and headache (1.7%). The incidence of other adverse events rose for this group. These include bronchitis (5.7% to 9.4%), pneumonia (0.8% to 2.6%), sinusitis (0.8% to 2.6%), cough (4.1% to 9.4%), and conjunctivitis NOS (1.6% to 3.4%).*

For those subjects who switched from vehicle to ASM 1% cream in the open-label phase (20 weeks), new treatment emergent adverse events include tonsillitis NOS (5.4%), croup infectious (5.4%), bronchitis acute NOS (3.6%), sore throat (3.6%), and many infections (e.g. herpes simplex dermatitis, hepatitis B, hand, foot and mouth, strep throat). Each of these occurred at an incidence of 1.8% (see table 44 for complete list). Other adverse events that rose after the switch to study drug (that have not been mentioned before) included bronchitis (4.8% to 8.9%), skin infection (1.6% to 3.6%), rhinitis (7.9% to 12.5%), dermatitis contact (1.6% to 7.1%), and food allergy (0 to 3.6%).

Other than what has already been discussed for local treatment emergent adverse events, there was a greater incidence of bacterial skin infection in the double-blind phase for the vehicle subjects than those on ASM 1% cream, 6.3% and 0.8%, respectively. This difference disappeared in the open-label phase as the disease of the patients in the vehicle arm responded

to treatment with ASM 1% cream (3.6% vehicle and 3.4% ASM 1% cream). The same can be said for application site irritation were it was much higher in the vehicle arm of the double-blind study, 4.8% and this difference disappeared in the open-label phase (<1% for both arms).

There were no clinically relevant laboratory abnormalities in this subject population that could be attributed to ASM 1% cream. These subjects did not receive skin anergy testing at the end of the 26-week trial.

The increased incidence of systemic infection that occurs in infants over 6 weeks in the ASM 1% cream arm as compared to vehicle, along with the increased incidence that is observed over a 6 month period, suggests that the safety profile for ASM 1% cream is sufficiently poor in this population to justify not recommending its use in infants to treat atopic dermatitis.

11.5a Sponsor's Protocol # CASM981 0315

Title: "A randomized, multicenter, parallel-group, double-blind, vehicle-controlled study to evaluate the efficacy and safety of SDZ ASM 981 cream in the long-term management of atopic dermatitis in children from 3 months to 23 months of age"

11.5a.1 Design/Protocol/Objective

All of these parameters are the same as for study B313 and are described under 11.6.1.1-3, page 82

11.5a.2 Safety Outcomes

As stated under "Description of Clinical Sources", this trial was not reviewed in detail. However, the pertinent adverse event profile that occurred in this trial is shown in table 46a as support for the position that infants have a significant increase in infection such that in this reviewer's opinion warrant that ASM 1% cream not be used in this age group for atopic dermatitis.

Table 46a
Incidence Rates of Common (≥2%) Treatment Emergent Adverse Events*
Safety Population

	ASM 1% (N=204) N (%)	Vehicle (N=46) N (%)	Treatment Difference and 95% CI*	
At least 1 AE	192(94.1)	44(95.7)	-16%	
At least 1 common AE	188(92.2)	44(95.7)	-35%	
Infections and infestations				
Nasopharyngitis	71 (34.8)	15 (32.6)	2.2%	
Upper Respiratory Tract Infection NOS	43 (21.1)	8 (17.4)	3.7%	
Chickenpox	15 (7.4)	2 (4.3)	3.0%	
Otitis Media NOS	15 (7.4)	2 (4.3)	3.0%	
Bronchitis NOS	13 (6.4)	2 (4.3)	2.0%	
Tonsillitis NOS	11 (5.4)	1 (2.2)	3.2%	
Viral Rash NOS	9 (4.4)	0	4.4%	(1.6%, 7.2%)
Lower Respiratory Tract Infection NOS	8 (3.9)	0	2.5%	(0.3%, 4.6%)
Influenza	7 (3.4)	1 (2.2)	1.3%	
Eye Infection NOS	5 (2.5)	0	2.5%	(0.3%, 4.6%)
Pharyngitis NOS	5 (2.5)	0	2.5%	(0.3%, 4.6%)
Respiratory Tract Infection NOS	5 (2.5)	0	2.5%	(0.3%, 4.6%)
General disorders and administration site conditions				
Pyrexia	61 (29.9)	9 (19.6)	10.3%	
Respiratory, thoracic and mediastinal disorders				
Cough	31 (15.2)	4 (8.7)	6.5%	
Rhinitis NOS	26 (12.7)	4 (8.7)	4.1%	
Asthma NOS	8 (3.9)	1 (2.2)	1.8%	
Rhinorrhea	8 (3.9)	0	3.9%	(1.3%, 6.6%)
Wheezing	8 (3.9)	0	3.9%	(1.3%, 6.6%)
Gastrointestinal disorders				
Teething	56 (27.5)	10 (21.7)	5.7%	
Vomiting NOS	19 (9.3)	2 (4.3)	5.0%	
Toothache	6 (2.9)	0	2.9%	(0.62%, 5.3%)
Eye Disorders				
Conjunctivitis NEC	11 (5.4)	1 (2.2)	3.2%	
Skin & Subcutaneous Tissue Disorders				
Urticaria	1 (0.3%)	1 (1.5%)	NS	
Acne NOS	1 (0.3%)	4 (1.5%)	NS	
Immune System Disorders				
Hypersensitivity NOS	17 (8.3)	1 (2.2)	6.2%	(0.5%, 11.8%)
Psychiatric Disorders				
Irritability	5 (2.5)	0	2.5%	(0.3%, 4.6%)

Source: Adapted from post-text table 10.1-2
*Confidence Interval if significant

Table 46a shows that the subjects in the ASM 1% arm continue to have a greater incidence of adverse events including nasopharyngitis, URIs, otitis media, pyrexia, bronchitis, tonsillitis, influenza, teething, cough, irritability, chickenpox, vomiting, rhinitis, asthma, dermatitis contact, and conjunctivitis. This table also demonstrates that there are adverse events that are now statistically significant in their occurrence in infants on ASM 1% cream after use over a 6 month period as compared to vehicle that were not present in the short-term 6 week vehicle controlled trial. These include viral rash (4.4% vs. 0), lower respiratory tract infection