8.4.1.4.2 Primary Efficacy Results:

A- Success in the General Population:

Results for success at the end of treatment are summarized for the two adult studies combined and for each adult study separately in Table 24.

Table 24: Success Rate at the End of Treatment

Study	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Intent-to-Treat Population			
Pediatric Study	8/116 (6.9%)	42/117 (35.9%)	48/118 (40.7%)
Efficacy Evaluable Population			
Pediatric Study	8/101 (7.9%)	39/108 (36.1%)	44/107 (41.1%)
Per Protocol Population			
Pediatric Study	7/83 (8.4%)	35/91 (38.5%)	40/100 (40.0%)

Source: Table 5 of ISE and Table 8 of individual study report as amended in 11/9/99 and 4/21/00 submissions.

Results for P values of differences in success at the end of treatment are summarized in Table 25.

Table 25: Test of Significance for Success Rate

	P-Value†			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Intent-to-Treat Population				
Pediatric Study	<0.001	<0.001	<0.001	0.401
Efficacy Evaluable Population				
Pediatric Study	<0.001	<0.001	<0.001	0.406
Per Protocol Population				
Pediatric Study	<0.001	<0.001	<0.001	0.755

Source: Table 6 of ISE and Table 9 of each individual study report as amended in 11/9/99 and 4/21/00 submissions.

Reviewer's Comments:

For all three populations (MITT, efficacy evaluable, and per protocol population), a statistically significant difference in success was observed among the three treatment groups. A significantly

greater success rate was observed for each tacrolimus ointment treatment group compared with the vehicle.

However, the results of this study failed to show any statistically significant greater success rate for the 0.1% tacrolimus ointment treatment group compared with the 0.03% tacrolimus ointment treatment group, although a trend can be observed (success rate with 0.1% - success rate with 0.03% = 1.5% to 5.0%, depending on the population studied, see table 24). The sponsor claims a statistically significant difference in the time to first at least slight improvement, being significantly shorter (p=0.039) in the 0.1% tacrolimus group compared with the 0.03% tacrolimus group (Appendix 14.2.2.5.1 of the study report). However, the time to first excellent, marked or moderate improvement was comparable between the two tacrolimus treatment groups. Also, the data in Table 14.3.5.2.1 (Appendix of the study report) show that this statistically significant difference in the mean time to first slight improvement is only 0.7/11.6 days, a clinically insignificant difference.

These results support efficacy of the both concentrations in the pediatric population, but fail to support any advantage of the higher potency.

B- Success by Population Subsets:

Success rates for **the ITT patient population** in the pediatric study are presented by age, gender, race, baseline disease severity, and percent body surface area affected at baseline in ISE Statistical Appendices 8.3.6.4.3, and are summarized in the following tables:

Table 26: Success Rate By Age

Age (Years)	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
2-6	4/72 (5.6%)	28/74 (37.8%)	33/69 (47.8%)
7-15	4/44 (9.1%)	14/43 (32.6%)	15/49 (30.6%)

Table 27: Test of Significance for Success Rate: Age

Age (Years)	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
2-6	<0.001	<0.001	<0.001	0.229
7-15	0.017	0.007	0.011	0.842

Table 28: Success Rate By Gender

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Males	3/53 (5.7%)	18/55 (32.7%)	25/57 (43.9%)
Females	5/63 (7.9%)	24/62 (38.7%)	23/61 (37.7%)

Table 29: Test of Significance for Success Rate: Gender

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Males	<0.001	<0.001	<0.001	0.146
Females	<0.001	<0.001	<0.001	0.905

Table 30: Success Rate By Race (White, Black, Oriental)

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
White	5/78 (6.4%)	30/76 (39.5%)	34/75 (45.3%)
Black	0/28 (0.0%)	8/32 (25.0%)	9/34 (26.5%)
Oriental	3/8 (37.5%)	3/7 (42.9%)	5/6 (83.3%)

Table 31: Test of Significance for Success: Race

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
White	<0.001	<0.001	<0.001	0.420
Black	0.014	0.006	0.004	0.861
Oriental	0.263	0.872	0.113	0.194

Table 32: Success Rate By Baseline Disease Severity

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Moderate	6/47 (12.8%)	20/45 (44.4%)	20/43 (46.5%)
Severe	2/69 (2.9%)	22/72 (30.6%)	28/75 (37.3%)

Table 33: Test of Significance for Success Rate: Baseline Disease Severity

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
Moderate	0.001	0.001	<0.001	0.727
Severe	<0.001	<0.001	<0.001	0.374

Table 34: Success By Percent BSA Affected at Baseline

	Treatment Group		
	Vehicle	**Concentration of Tacrolimus Ointmen**	
		0.03%	**0.1%**
10-≤25%	4/33 (12.1%)	18/41 (43.9%)	11/27 (40.7%)
>25-≤50%	4/30 (13.3%)	11/27 (40.7%)	19/36 (52.8%)
>50-≤75%	0/25 (0.0%)	10/28 (35.7%)	14/34 (41.2%)
>75-100%	0/28 (0.0%)	3/21 (14.3%)	4/21 (19.0%)

Table 35: Test of Significance for Success Rate: Percent BSA Affected at Baseline

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
10-≤25%	0.009	0.003	0.024	>0.999
>25-≤50%	0.004	0.020	0.001	0.376
>50-≤75%	0.001	0.001	<0.001	0.598
>75-100%	0.065	0.030	0.021	0.685

Reviewer's Comments:

The results in Tables 26-35 demonstrate that:

1- The number of oriental subjects is very small (6 to 8 in each arm) resulting in failure to show effectiveness of either 0.03% or 0.1% formulations.

2- In all sub-populations, except for the oriental race, both the 0.03% and 0.1% formulations were significantly better than placebo.

3- The 0.1% formulation is not significantly better than the 0.03% formulation in any of sub-populations tested. However, it is to be noted that all (Adult and pediatric) 12 week controlled studies in this NDA were not powered to detect significant differences between the two concentrations of Tacrolimus ointment.

C- Success by Study Sites:

There was a statistically significant treatment by center interaction with respect to success rate. Table 14.2.2.1.1 (NDA, section 8.1.1.1) shows the success rate at the end of treatment by center.

Reviewer's Comments:

The results in Table 14.2.2.1.1 did not show any center with higher success of placebo in comparison to the 0.03% or the 0.1% ointments in any of the centers. The small numbers in each center is the most likely reason for the noticeable variation between centers.

8.4.1.4.3 Secondary Efficacy Results

The protocol-specified secondary efficacy variables included the change from baseline to the end of treatment for the Eczema Area and Severity Index (EASI), percentage of body surface area affected (% BSA), the Physician's Assessment of Individual Signs of Atopic Dermatitis, the Patient's Assessment of Treatment Effects (Overall Response and Pruritus), and the incidence of recurrence. Certain of these secondary efficacy variables may be relevant to the labeling and will be discussed in this review.

A- Reduction in percentage of body surface area affected (% BSA)

The change from baseline to the end of treatment in the percentage of affected body surface area in the ITT population is presented in the following 2 tables.

Table 36: Change from Baseline to the End of Treatment: Affected Body Surface Area

Least Square Mean ± SE	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Pediatric Study	N=116	N=117	N=118
Change from Baseline	-6.4 ± 1.98	-26.4 ± 1.90	-27.5 ± 1.91

Patient Population: Modified intent-to-treat; all randomized patients who received at least one dose of study drug (= all patients who were dispensed study drug).
Source: Section 8.3.6 (ISE Statistical Appendix 8.3.6.7.3).

Table 37: Test of Significance for Change from Baseline in Affected Body Surface Area

	P-Value from General Linear Model Analysis†			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
Pediatric Study	<0.001	<0.001	<0.001	0.664

Patient Population: Modified intent-to-treat; all randomized patients who received at least one dose of study drug (= all patients who were dispensed study drug).
† Statistical significance is indicated by p-values ≤0.05.
Source: Section 8.3.6 (ISE Statistical Appendix 8.3.6.7.3).

Reviewer's Comments:

Statistically significantly greater improvement was observed for each tacrolimus ointment treatment group compared with the vehicle group. A statistically significant difference between tacrolimus ointment treatment groups was not observed in this study.

Improvement was observed as early as Week 1 in the tacrolimus treatment groups. Throughout the study duration, greater decreases in the percentage of affected body surface area were observed for each tacrolimus treatment group compared with the vehicle group (see NDA: ISE Statistical Appendix 8.3.6.8.3).

B- Reduction in physician assessment of individual signs

The Change from Baseline to the End of Treatment for Individual Signs of Atopic Dermatitis (ITT Population), and the results of the test of significance for Individual Signs (ITT Population), are shown in tables 38 and 39, respectively.

Table 38: Change from Baseline to the End of Treatment for Individual Signs of Atopic Dermatitis: Intent to Treat Population

Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Edema			
N	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.7 ± 0.06	-0.8 ± 0.06
Erythema			
N	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.06	-0.8 ± 0.06
Excoriation			
N	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.7 ± 0.06	-0.9 ± 0.06
Lichenification			
N	116	117	118
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.05	-0.7 ± 0.05
Oozing			
N	116	117	118
Least Squares Mean ± SE	-0.0 ± 0.05	-0.5 ± 0.05	-0.5 ± 0.05
Scaling			
N	116	1317	118
Least Squares Mean ± SE	-0.3 ± 0.06	-0.9 ± 0.06	-1.0 ± 0.06

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug.

SE: standard error. Source: Integrated Summary of Effectiveness Appendix 8.3.6.7.3

Table 39: Test of Significance for Individual Signs of Atopic Dermatitis: Intent to Treat Population

Parameter	General Linear Model Analysis p-Values			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Edema	<0.001	<0.001	<0.001	0.712
Erythema	<0.001	<0.001	<0.001	0.712
Excoriation	<0.001	<0.001	<0.001	0.152
Lichenification	<0.001	<0.001	<0.001	0.448
Oozing	<0.001	<0.001	<0.001	0.920
Scaling	<0.001	<0.001	<0.001	0.509

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug. [One patient randomized to vehicle was never dispensed study drug; therefore modified intent-to-treat definition = FDA intent-to-treat definition].
Source: Integrated Summary of Effectiveness Appendix 8.3.6.7.3

Reviewer's Comments:

The sponsor's analysis in each trial report as well as in the ISE was limited to the total of the individual scores, although the proposed label includes [redacted] Therefore, tables 38 and 39 had to be compiled by the reviewer from the table in Appendix 8.3.6.7.3 of the ISE of the NDA.

The representative score for each of the six clinical signs, edema, erythema, excoriation, lichenification, oozing, and scaling, was defined as the sum of the individual scores for all body regions treated at baseline divided by the number of regions treated at baseline. As shown in tables 38 and 39, the results obtained for each of the six individual signs of atopic dermatitis showed significantly greater improvements in the 0.03% and the 0.1% tacrolimus ointment group compared to the venicle. However, comparison of the 0.1% tacrolimus ointment group with the 0.03% tacrolimus ointment group failed to show any significant differences in the representative scores.

C- *Patient's assessment of treatment effects*

The treatment effects evaluated by the patients included the overall response and pruritus. Although both were included in the secondary efficacy criteria, the sponsor did not discuss the results of pruritus assessment by the patients for the ITT or MITT populations in the individual study reports (main text) or in the ISE.

The results of the patient's assessment of overall response were presented in the NDA, section 8.3.6 (ISE Statistical Appendix 8.3.6.6.3). These results were discussed in the NDA section 8.3.3.9 (ISE) and were summarized in table 25 of this section. Statistically significant differences were observed among treatment groups for the pediatric study ($p<0.001$ for each;

CMH statistics testing for row mean score difference); statistically significant differences between each tacrolimus ointment group and vehicle were also observed ($p<0.001$ for each). No statistically significant differences were observed between 0.1% tacrolimus ointment and 0.03% tacrolimus.

Reviewer's Comments

The results of the patient's assessment of overall response are in general agreement with the primary efficacy variable.

The following table of the change in patient's assessment of pruritus has been compiled by the reviewer from the NDA statistical appendix 8.3.6.7.3 (ISE).

The differences shown in this table between the 0.03% or the 0.1% tacrolimus ointments and the vehicle were statistically significant, but the differences between the 0.03% and the 0.1% tacrolimus ointments were not statistically significant.

Table 40: Change from Baseline to the End of Treatment for Patient's Assessment of Pruritus: Intent to Treat Population

Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Protocols 97-0-037			
N	116	116	116
Least Squares Mean ± SE	-0.8 ± 0.30	-3.9 ± 0.29	-3.9 ± 0.29

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug.
Source. Integrated Summary of Effectiveness Appendix 8.3.6.7.3.

D- Recurrences

Reviewer's Comments:

Although recurrences were one of the secondary efficacy variables, they were not discussed by the sponsor in the individual study reports or in the ISE. The data, however, were presented in tables 14.3.5.6.1,2 in the statistical appendix of the report on this study. The number of patients who had documented recurrences after being successfully treated (90% improvement or more) were 20/37 i.e. **54%** in the 0.03% tacrolimus arm and 22/42 i.e. **52%** in the 0.1% tacrolimus arm. These recurrences occurred as early as 1 day, and as late as 22 days (mean = **8.3 days**) after discontinuation of treatment. This information is recommended for inclusion in the label.

8.4.2. Trial #2: 96-0-025

8.4.2.1 Objective/Rationale

The primary objective of this study was to assess the safety of tacrolimus ointment when used continuously or intermittently for up to 1 year in pediatric patients (2 to <16 years) with moderate to severe atopic dermatitis. In addition, long-term efficacy was evaluated based on patient's and physician's assessments.

8.4.2.2 Design

This was a phase 3, open-label, single-concentration (0.1%), multi-center, long-term study. Patients were evaluated at least six times during the 1-year study period: at baseline (Day 1), Week 1, and Months 3, 6, 9, and 12 or end of study, if less than 12 months. Scheduled evaluations were performed regardless of whether the disease was active or in remission. Adverse events were monitored on an ongoing basis. Blood and urine were to be collected on Day 1 and at Months 6 and 12/end of study in order to determine laboratory profiles.

Reviewer's Comments:

This study is uncontrolled and open. Its relevance for efficacy evaluation is therefore very limited. Being the only pivotal phase 3 long-term study, this study will be evaluated only for relevance to long term efficacy of the drug.

8.4.2.3 Study Results

8.4.2.3.1 Long-term Efficacy

In this study, 219 patients were on study for at least 6 months and 180 patients were on study for 12 months. The efficacy parameters for this long-term study are presented by study visit in the NDA, ISE, section 8.3.6 (ISE Statistical Appendix 8.3.6.9.1).

In this study, patients showed a rapid improvement (within 1 week) in their disease status. Improvement was evidenced by reductions in the percent body surface area affected and EASI score (Tables 41, 42); improvement was also observed for the patient's and physician's assessment of global response and patient's assessment of itch. Improvement of atopic dermatitis was apparent after one week of treatment with 0.1% tacrolimus ointment and maximal improvement (Month 3) was maintained for the remainder of the study. There was no evidence of loss of effectiveness over time.

Table 41: Efficacy Variables By Visit: Ages 2-6 years

Parameter	N	Mean ± SE	N	Change from Baseline (Mean ± SE)
% BSA Affected				
Day 1	115	42.7 ± 2.5	—	—
Week 1	111	35.3 ± 2.5	111	-7.4 ± 1.2
Month 3	101	22.4 ± 2.5	101	-19.3 ± 1.9
Month 6	77	20.5 ± 2.9	77	-21.0 ± 2.4
Month 12	63	18.1 ± 2.5	63	-27.4 ± 2.8
EASI Score				
Day 1	115	19.8 ± 1.2	—	—
Week 1	110	11.4 ± 1.0	110	-8.4 ± 0.7
Month 3	101	7.7 ± 0.9	101	-12.4 ± 1.0
Month 6	77	6.5 ± 0.9	77	-14.2 ± 1.2
Month 12	63	5.7 ± 0.8	63	-15.9 ± 1.4

Patient Population: all enrolled patients who received at least one dose of study drug and had post-baseline data. SD: standard deviation. BSA: body surface area.
EASI: Eczema Area and Severity Index; composite of severity grade in Physician's Assessment for four individual signs and adjusted percentage of affected body surface area. Highest possible score is 72.
Source: NDA, ISE, Table 27; and section 8.3.6 (ISE Statistical Appendix 8.3.6.9.1).

Table 42: Efficacy Variables By Visit: Ages 7-15 years

Parameter	N	Mean ± SE	N	Change from Baseline (Mean ± SE)
% BSA Affected				
Day 1	140	39.4 ± 2.0	—	—
Week 1	139	32.9 ± 2.0	139	-6.7 ± 0.9
Month 3	130	20.3 ± 2.1	130	-18.9 ± 1.7
Month 6	77	18.8 ± 2.2	111	-19.4 ± 1.9
Month 12	93	14.7 ± 2.1	93	-23.8 ± 2.1
EASI Score				
Day 1	140	19.6 ± 1.1	—	—
Week 1	139	12.7 ± 0.9	139	-7.0 ± 0.5
Month 3	130	7.7 ± 0.9	130	-11.7 ± 0.8
Month 6	111	7.6 ± 1.0	111	-12.2 ± 1.1
Month 12	93	5.7 ± 0.8	93	-13.6 ± 1.0

Patient Population: all enrolled patients who received at least one dose of study drug and had post-baseline data. SD: standard deviation. BSA: body surface area.
EASI: Eczema Area and Severity Index; composite of severity grade in Physician's Assessment for four individual signs and adjusted percentage of affected body surface area. Highest possible score is 72.
Source: NDA, ISE, Table 27; and section 8.3.6 (ISE Statistical Appendix 8.3.6.9.1).

Reviewer's Comments:

The results presented in Tables 41 and 42 show maintenance, or slowly progressive improvement, of the averages of measurements indicative of effective treatment of the atopic dermatitis patients over 6 and 12 months of treatment. However, no data were presented or discussed, either in the individual study report or the ISE, regarding recurrence or relapse rates. However, evaluation of the episodes in this study was provided in the Appendix to this study report (Tables 14.3.9.1-4, and 14.3.9.6.1,2 in the NDA). These tables provide data for 40 (16%) patients that had more than one episode (i.e. cleared, discontinued treatment and then relapsed into a second episode, etc.). In brief, 32 of these 40 patients experienced 2 episodes, 5 patients experienced three episodes, one patient experienced 4 episodes, and 2 patients experienced 5 episodes each. The mean time to recurrence for these 40 patients was 54.5 days (SD = 53.8 days) following the first episode and ranged between 32 and 37 days following subsequent treatment episodes

An additional measure of the long-term effectiveness of treatment, relapse or recurrence rates may be indicated by the days of treatment, the usage of the ointment, or the %BSA treated at different times. This additional measure is important because of its value for comparison of the results of this trial with the results of the similar long-term study in the adults (in FG-06-12, though similarly designed, recurrences or episode analyses were not provided). Tables for these parameters were provided in the appendix of the study report (tables 13.3.1-3). The protocol of this study allowed patients to change the treatment areas or select new ones on the basis of the presence of itch, although the initial treatment area was selected by the investigator on day 1. Also, patients were instructed to continue application of the ointment for one week after itch had resolved (see NDA, section 8.2.1.1, treatment administration [section 5.3.1]).

The results presented in these tables (NDA, section 8.2.1.1, tables 13.3.1-3) show a general decrease in total treated BSA from week 1 to month 3. This was maintained or slightly improved up till month 12 (tables 13.3.2&3). Table 13.3.1 shows that the enrolled patients were without treatment for **12.9%** of the total days they were in the study (36.0/315.3). This information was based ~~on~~ the patients' diaries.

It may be concluded from these results that patients will need treatment, almost all the time (>85% of the time), to maintain the improvement in their atopic dermatitis signs and symptoms that was achieved by the initial treatment with 0.1% tacrolimus ointment.

8.5 Review of safety:

8.5.1 Three Pivotal Controlled Studies

8.5.1.1 Exposure

The degree of atopic dermatitis involvement at baseline for patients in the three pivotal studies is presented in Section 8.4.13 of the NDA (ISS Statistical Appendices 8.4.13.2.1, 8.4.13.2.2, 8.4.13.2.3, 8.4.13.2.4, 8.4.13.2.5, 8.4.13.2.6, 8.4.13.2.7, 8.4.13.2.8, 8.4.13.2.9, 8.4.13.2.10, and 8.4.13.2.11).

The mean percent body surface area affected at baseline was 46% (range: 10% to 100%) for the overall population in the three pivotal studies and was comparable among treatment groups. The mean percent body surface area treated at the start of therapy was also comparable among treatment groups. Nearly all (>98%) areas affected at baseline were treated at the start of therapy.

8.5.1.1.1 Treatment Days

Study drug use, including the number of treatment days for patients in the three pivotal studies is presented in Section 8.4.13 of the NDA (ISS Statistical Appendices 8.4.13.3.1, 8.4.13.3.2, 8.4.13.3.3, 8.4.13.3.4, 8.4.13.3.5, 8.4.13.3.6, 8.4.13.3.7, 8.4.13.3.8, 8.4.13.3.9, 8.4.13.3.10, and 8.4.13.3.11).

The mean (median) number of treatment days was 43 (25.5) in the vehicle treatment group and 70 (84, 0.03%; 85, 0.1%) in each of the tacrolimus ointment treatment groups. There were no notable age differences in the length of treatment in the tacrolimus ointment treatment groups. The lower number of treatment days in the vehicle group is due to the higher percentage of premature discontinuations in the vehicle group (primarily due to lack of efficacy) compared with the tacrolimus groups. Treatment days for the three pivotal studies are summarized in Table 43.

Table 43: Treatment Days: Three Pivotal Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
All Patients	**N**	328	328	325‡
	Mean ± SD	43.2 ± 34.8	70.5 ± 26.8	70.1 ± 28.7
	Median	25.5	84.0	85.0
	Range			
Pediatric Patients†	**N**	116	118	118
	Mean ± SD	49.1 ± 34.7	72.4 ± 26.9	73.6 ± 26.5
	Median	46.5	85.0	85.0
	Range			
2-6 years of age	***N***	*72*	*74*	*69*
	Mean ± SD	*50.6 ± 35.5*	*72.3 ± 26.8*	*72.0 ± 28.1*
	Median	*63.5*	*85.0*	*84.0*
	Range			
7-15 years of age†	***N***	*44*	*44*	*49*
	Mean ± SD	*46.6 ± 33.6*	*72.6 ± 27.3*	*76.0 ± 24.1*
	Median	*25.5*	*85.0*	*85.0*
	Range			
Adult Patients	**N**	212	210	207‡
	Mean ± SD	40.0 ± 34.5	69.4 ± 26.8	68.1 ± 29.7
	Median	22.0	84.0	84.0
	Range			

Patient population: all randomized patients who received at least one dose of study drug.
SD: standard deviation.
† Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
‡ Two patients did not have complete treatment day information.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendices 8.4.13.3.1, 8.4.13.3.2, 8.4.13.3.3, 8.4.13.3.4, and 8.4.13.3.5; for appendix titles see List of Appendices).

8.5.1.1.2 Ointment Use

Study drug use for patients in the three pivotal studies is presented in Section 8.4.13 of the NDA (ISS Statistical Appendices 8.4.13.3.1, 8.4.13.3.2, 8.4.13.3.3, 8.4.13.3.4, 8.4.13.3.5, 8.4.13.3.6, 8.4.13.3.7, 8.4.13.3.8, 8.4.13.3.9, 8.4.13.3.10, and 8.4.13.3.11).

The mean total amount of ointment used during the three pivotal studies was 272 grams (range — grams) for the vehicle group, compared with 381 grams (range — grams) and 390 grams (range — grams) for the 0.03% and 0.1% tacrolimus ointment treatment groups, respectively. This represents a mean total amount of tacrolimus applied of 114 mg (range — mg) and 390 mg (range — mg) in the 0.03% and 0.1% tacrolimus ointment treatment groups, respectively.

Generally, the amount of ointment used by children (2-15 years of age) was lower than for adults (≥16 years of age). Similarly, younger children (2-6 years of age) used less ointment than older children (7-15 years of age). The lower amount of ointment used in children is likely due to their smaller body size, even though the percentage of body surface area treated was similar (Section 8.4.13 of the NDA, ISS Statistical Appendices 8.4.13.2.2, 8.4.13.2.3, 8.4.13.2.4, and 8.4.13.2.5).

The daily ointment use in vehicle-treated patients was higher than in tacrolimus ointment-treated patients since the majority of vehicle-treated patients discontinued early in the study when the percent affected body surface area was the highest. In contrast, mean daily ointment use for tacrolimus ointment-treated patients is averaged over a longer period of time when percent affected body surface area was decreasing. Daily ointment use is presented in Table 44.

Table 34: Daily Ointment Use (Grams): Three Pivotal Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
All Patients	N	274	264	249
	Mean ± SD	8.8 ± 8.9	5.6 ± 5.2	5.6 ± 5.1
	Median	5.6	4.0	4.0
	Range			
Pediatric Patients‡	N	95	93	90
	Mean ± SD	7.4 ± 6.3	4.5 ± 4.4	4.1 ± 3.5
	Median	4.8	3.1	3.3
	Range			
2-6 years of age	*N*	*61*	*58*	*52*
	Mean ± SD	*6.7 ± 5.3*	*4.2 ± 3.5*	*3.9 ± 3.3*
	Median	*4.6*	*3.2*	*3.0*
	Range			
7-15 years of age‡	*N*	*34*	*35*	*38*
	Mean ± SD	*8.6 ± 7.9*	*5.1 ± 5.5*	*4.4 ± 3.8*
	Median	*6.0*	*3.1*	*3.6*
	Range			
Adult Patients	N	179	171	159
	Mean ± SD	9.6 ± 10.0	6.2 ± 5.5	6.4 ± 5.7
	Median	6.3	4.5	4.7
	Range			

Patient population: all randomized patients who received at least one dose of study drug and returned all tubes at all visits. SD: standard deviation.

‡ Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.

† Patient No. 14607 in Study 97-0-036 was treated for 2 days; however, the difference in tube weight (dispensed-returned) was recorded as 0.

Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).

Source: Section 8.4.13 (ISS Statistical Appendices 8.4.13.3.1, 8.4.13.3.2, 8.4.13.3.3, 8.4.13.3.4, and 8.4.13.3.5; for appendix titles see List of Appendices).

8.5.1.1.3 Tacrolimus Blood Concentrations

Tacrolimus blood concentrations for patients in the three pivotal studies are summarized in Section 8.4.13 of the NDA (ISS Statistical Appendices 8.4.13.4.1, 8.4.13.4.2, 8.4.13.4.3, 8.4.13.4.4, 8.4.13.4.5, 8.4.13.4.6, 8.4.13.5.1, 8.4.13.5.2, 8.4.13.5.3, 8.4.13.5.4, 8.4.13.5.5, and 8.4.13.5.6). Sampling to measure tacrolimus blood concentrations occurred randomly relative to the time of tacrolimus ointment application. Thus, the blood concentrations measured below are neither peak nor trough values.

The distribution of, and descriptive statistics for tacrolimus blood concentrations are presented in Table 45-A and Table 45-B, respectively.

Table 45-A: Distribution of Patients with Maximum Tacrolimus Blood Concentrations within a Selected Range: Three Pivotal Studies

Number of Patients with Highest Individual Concentration Within the Indicated Range Anytime During Treatment		Concentration of Tacrolimus Ointment 0.03%		0.1%	
All Patients	N	220		223	
	<LOQ	159	(72.3%)	138	(61.9%)
	LOQ-<1 ng/mL	42	(19.1%)	47	(21.1%)
	1-<2 ng/mL	12	(5.5%)	25	(11.2%)
	2-<5 ng/mL	5	(2.3%)	12	(5.4%)
	≥5 ng/mL	2	(0.9%)	1	(0.4%)
Pediatric Patients†	N	26		30	
	<LOQ	23	(88.5%)	24	(80.0%)
	LOQ-<1 ng/mL	2	(7.7%)	4	(13.3%)
	1-<2 ng/mL	1	(3.8%)	1	(3.3%)
	2-<5 ng/mL	0		1	(3.3%)
	≥5 ng/mL	0		0	
2-6 years of age	N	16		17	
	<LOQ	13	(81.2%)	11	(64.7%)
	LOQ-<1 ng/mL	2	(12.5%)	4	(23.5%)
	1-<2 ng/mL	1	(6.2%)	1	(5.9%)
	2-<5 ng/mL	0		1	(5.9%)
	≥5 ng/mL	0		0	
7-15 years of age†	N	10		13	
	<LOQ	10	(100.0%)	13	(100.0%)
	LOQ-<1 ng/mL	0		0	
	1-<2 ng/mL	0		0	
	2-<5 ng/mL	0		0	
	≥5 ng/mL	0		0	
Adult Patients	N	194		193	
	<LOQ	136	(70.1%)	114	(59.1%)
	LOQ-<1 ng/mL	40	(20.6%)	43	(22.3%)
	1-<2 ng/mL	11	(5.7%)	24	(12.4%)
	2-<5 ng/mL	5	(2.6%)	11	(5.7%)
	≥5 ng/mL	2	(1.0%)	1	(0.5%)

Patient population: all randomized patients who received at least one dose of study drug and had blood collected during treatment for tacrolimus concentration determination.

LOQ: lower limit of quantitation. Tacrolimus blood concentrations were determined using a [redacted] method with a LOQ of [redacted] ng/mL.

† Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.

Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).

Source: Section 8.4.13 (ISS Statistical Appendices 8.4.13.5.1, 8.4.13.5.2, 8.4.13.5.3, 8.4.13.5.4, and 8.4.13.5.5; for appendix titles see List of Appendices).

Table 45-B: Tacrolimus Blood Concentrations (ng/mL): Three Pivotal Studies

		Treatment Group	
		Concentration of Tacrolimus Ointment	
		0.03%	0.1%
All Patients			
Week 1	**N**	197	202
	Mean ± SD	0.22 ± 0.85	0.31 ± 0.70
	Median	0	0
	Range		
Week 3	**N**	174	180
	Mean ± SD	0.12 ± 0.36	0.29 ± 0.65
	Median	0	0
	Range		
Week 12	**N**	126	137
	Mean ± SD	0.19 ± 0.48	0.18 ± 0.49
	Median	0	0
	Range		
Pediatric Patients†			
Week 1	**N**	22	26
	Mean ± SD	0.08 ± 0.27	0.16 ± 0.35
	Median	0	0
	Range		
Week 3	**N**	21	26
	Mean ± SD	0.03 ± 0.15	0.20 ± 0.51
	Median	0	0
	Range		
Week 12	**N**	16	18
	Mean ± SD	0.04 ± 0.16	0.10 ± 0.42
	Median	0	0
	Range		

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(Table continued)

		Treatment Group	
		Concentration of Tacrolimus Ointment	
		0.03%	0.1%
2-6 years of age			
Week 1	N	13	15
	Mean ± SD	0.13 ± 0.35	0.28 ± 0.43
	Median	0	0
	Range		
Week 3	N	12	13
	Mean ± SD	0.06 ± 0.20	0.40 ± 0.67
	Median	0	0
	Range		
Week 12	N	11	10
	Mean ± SD	0.06 ± 0.19	0.18 ± 0.57
	Median	0	0
	Range		
7-15 years of age†			
Week 1	N	9	11
	Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
	Median	0	0
	Range		
Week 3	N	9	13
	Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
	Median	0	0
	Range		
Week 12	N	5	8
	Mean ± SD	0.00 ± 0.00	0.00 ± 0.00
	Median	0	0
	Range		

Table continued on next page

(Table continued)

		Treatment Group	
		Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Adult Patients			
Week 1	**N**	175	176
	Mean ± SD	0.24 ± 0.90	0.33 ± 0.73
	Median	0	0
	Range	[redacted]	[redacted]
Week 3	**N**	153	154
	Mean ± SD	0.13 ± 0.37	0.31 ± 0.67
	Median	0	0
	Range	[redacted]	[redacted]
Week 12	**N**	110	119
	Mean ± SD	0.22 ± 0.51	0.20 ± 0.50
	Median	0	0
	Range	[redacted]	[redacted]

Patient population: all randomized patients who received at least one dose of study drug and had blood collected during treatment for tacrolimus concentration determination.
LOQ: lower limit of quantitation. Tacrolimus blood concentrations were determined using a [redacted] method with a LOQ of — ng/mL. Values below LOQ were considered to be zero.
† Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendices 8.4.13.4.1, 8.4.13.4.2, 8.4.13.4.3, 8.4.13.4.4, and 8.4.13.4.5; for appendix titles see List of Appendices).

Tacrolimus blood concentrations observed in the three pivotal studies are consistent with minimal absorption of drug through diseased skin following topical application. A total of 297 of 443 (67%) patients in the tacrolimus treatment groups (84% of pediatric patients and 65% of adults) who had blood samples collected during treatment had no quantifiable tacrolimus blood concentration (i.e., concentrations were below — ng/mL). For those patients with quantifiable levels, the indication was that such concentrations:

- decreased over treatment time. (Studies 97-0-037, 97-0-035, and 97-0-036, Appendix 14.4.2.3).

- were minimal compared with those following oral or intravenous administration.
  Based on a comparison of $AUC_{0\text{-}24}$ data from pharmacokinetic Study 94-0-008 with historical data after oral and IV administration to healthy volunteers, the relative

bioavailability of topically applied tacrolimus in adult and pediatric atopic dermatitis patients is estimated to be <5%; the absolute bioavailability is <0.5% (see also Section 6 of the NDA). The blood concentration data obtained in the pivotal studies are consistent with these estimates.

Following topical administration in atopic dermatitis patients, blood concentrations of ≥5 ng/mL were rarely (<1%) observed and were isolated events. In contrast, organ transplant patients typically are maintained for a lifetime on targeted trough concentrations of 5-15 ng/mL.

- were more often seen in adult patients than in pediatric patients. In the three pivotal studies, a lower percentage of pediatric patients had quantifiable blood concentrations (16%), and the highest individual concentration (→ ng/mL) was lower, than in adult patients (35%; ng/mL, respectively).

Reviewer's Comments:

The reviewer agrees in general with the sponsor's conclusions in this section (8.5.1.1). However, it seems that the distribution of the Tacrolimus blood concentrations needs further investigation. Approximately one third of the population tested (146/443) showed detectable blood levels, up to ng/mL. On examination of Listings (or Appendix) 14.4.2.3 of the individual studies reports, the reviewer found that: 1) in adults with any blood level 2 ng/mL or higher, 47% had detectable levels in all samples tested (normally 3 samples per patient, at weeks 1, 3 and 12) and 47% had detectable levels in 2 out of 3 samples tested, 2) in children with any blood level 1 ng/mL or higher (3 patients), one had detectable levels in all samples tested (3 samples) and one had detectable levels in 2 out of 3 samples tested.

Beyond the finding that all patients at ages 7-15 that has been tested (23 patients) did not have any detectable blood levels at any point of time, we do not see any indicator that can help to predict patients who do not show any blood levels and others who tend to show high blood levels in most of their blood samples. It is clear from Tables 45-A and 45-B that adult patients and pediatric patients 2-6 years old treated with 0.1% Tacrolimus ointment tend to have higher blood levels than those treated with the 0.03% formulation.

Due to the importance of the blood levels in the production of systemic toxicity of delayed onset, e.g. kidney damage or lymphomas, further data analysis was requested from the sponsor (teleconference on 10/26/00). Specifically, data base analysis including age, % BSA and severity at baseline, head and neck involvement, physician global evaluation on the week of blood sampling, and the Tacrolimus blood concentrations in these samples for all patients (n = 146) having detectable Tacrolimus blood concentrations in any of their blood samples.

The sponsor provided the data requested in a submission dated 11/10/00. Review of the database analysis confirmed the general lack of predictors for patients that may get high blood levels. For example, the set of patients (15 patients with 49 blood samples) who were **2-3 years of age** and had no detectable Tacrolimus blood levels in any of their blood samples included male (55%) and female patients with body surface areas (at baseline) ranging from **0.73 to 0.54 sq. m**. This set also included patients treated with 0.1% Tacrolimus ointment (20/49 samples, 7 from patients with moderate atopic dermatitis, and 13 from patients with severe atopic dermatitis) as well as patients treated with 0.03% Tacrolimus ointment (29/49 samples, 14 from patients with moderate atopic dermatitis, and 15 from patients with severe atopic dermatitis). The corresponding set of patients (3 patients with 14 blood samples) who were **2-3 years of age** and had detectable (max. = —— ng/mL) Tacrolimus blood levels in some (4/14) of their blood samples included only male patients with body surface areas (at baseline) ranging from **0.67 to 0.52 sq. m**. This set also included patients treated with 0.1% Tacrolimus ointment (one patient with 6 samples) as well as patients treated with 0.03% Tacrolimus ointment (two patients with 8 samples). All 3 patients in this set had severe atopic dermatitis at baseline.

Another example: The set of **adult patients** (250 patients with 940 blood samples, ages ranged from 17 to 79 years) who had no detectable Tacrolimus blood levels in any of their blood samples included male (38%) and female patients with body surface areas (at baseline) ranging from **2.67 to 1.32 sq. m**. This set also included patients treated with 0.1% Tacrolimus ointment (45% including patients with moderate and severe atopic dermatitis) as well as patients treated with 0.03% Tacrolimus ointment (55%, including patients with moderate and severe atopic dermatitis). The corresponding set of **adult patients** (137 patients with 509 blood samples, ages ranged from 17 to 77 years) who had detectable Tacrolimus blood levels (max = — ng/mL) in some of their blood samples (15.5% of blood samples were 1 ng/mL or above, and 38.5% of blood samples were 0.05 ng/mL or above) included male (53%) and female patients with body surface areas (at baseline) ranging from **2.93 to 1.35 sq. m**. This set also included patients treated with 0.1% Tacrolimus ointment (58% including patients with moderate and severe atopic dermatitis) as well as patients treated with 0.03% Tacrolimus ointment (42% including patients with moderate and severe atopic dermatitis). Only a slightly higher percentage of patients treated with 0.1% Tacrolimus ointment is noticed in the set with detectable blood levels (58%) in comparison with the set that had no detectable blood levels (45%). Also, a slightly higher percentage of males is noticed in the set with detectable blood levels (55%) in comparison with the set that had no detectable blood levels (38%).

The set of data for blood samples of all patients that had no Tacrolimus blood levels detectable at any time included 593/1130 (52%) samples from patients with severe atopic dermatitis at baseline. The set of data for blood samples of all patients that had detectable Tacrolimus blood levels at any time included 394/552 (71%%) samples from patients with severe atopic dermatitis at baseline. Again there is preponderance of patients with severe atopic dermatitis in the set with detectable blood levels, but a considerable percentage (52%) of patients with severe atopic dermatitis did not have any blood levels detected at any time.

8.5.1.2 *Adverse Events (Raw Incidence)*

8.5.1.2.1 Overall Adverse Events

A summary of the adverse events occurring during the treatment period (treatment emergent) for the three pivotal studies combined is presented in Table 45.

Table 46: Summary of the Raw Incidence of Treatment Emergent Adverse Events: Three Pivotal Studies

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Number of Patients	N=328	N=328	N=327
Overall AE	239 (72.9%)	286 (87.2%)	274 (83.8%)
Overall Drug-Related AE	168 (51.2%)	233 (71.0%)	217 (66.4%)
Application Site AE	178 (54.3%)	241 (73.5%)	229 (70.0%)
Nonapplication Site AE	154 (47.0%)	202 (61.6%)	195 (59.6%)
Infection†	116 (35.4%)	162 (49.4%)	157 (48.0%)
Serious Adverse Event	5 (1.5%)	2 (0.6%)	9 (2.8%)
AE Resulting in Discontinuation‡	35 (10.7%)	19 (5.8%)	14 (4.3%)

Patient population: all randomized patients who received at least one dose of study drug.
AE: adverse event. A patient could have had more than one adverse event.
Drug-related: possibly or probably related by investigator assessment. Missing relationship was considered *related.*
† Based on infection cluster (predefined cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc.) (Studies 97-0-037, 97-0-035, and 97-0-036; Appendix 14.4.4.2).
‡ Four patients in the adult studies (one in the vehicle treatment group, one in the 0.03% tacrolimus ointment treatment group and two in the 0.1% tacrolimus ointment treatment group) discontinued due to pregnancy; pregnancy was recorded as an adverse event due to Fujisawa Healthcare, Inc. administrative convention. These patients are not included as having discontinued due to an adverse event in this table.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.1.1, 8.4.13.6.2.1, 8.4.13.6.3.1, 8.4.13.6.4.1, 8.4.13.6.5.1, 8.4.13.6.6.1, and 8.4.13.6.7.1.

The overall incidence of treatment emergent adverse events in the three pivotal studies is presented in the NDA, Section 8.4.13 of the ISS (ISS Statistical Appendix 8.4.13.6.1.1).

The more common adverse events (those occurring in at least 5% of patients in any treatment group for the three pivotal studies combined) included flu-like symptoms (*flu syndrome*, a cluster of events including cold, congestion, common cold, influenza, upper respiratory infection, etc.), fever, allergic reaction, headache, increased cough, asthma, pruritus, the sensation of skin burning, skin erythema, and skin infection. The raw incidence of these adverse events in the three pivotal studies combined is presented in Table 47.

Table 47: Summary of the Raw Incidence of Individual Adverse Events†: Three Pivotal Studies

		Treatment Group					
		Vehicle		Concentration of Tacrolimus Ointment			
				0.03%		0.1%	
Number of Patients		N=328		N=328		N=327	
Body As a Whole	Flu Syndrome	41	(12.5%)	69	(21.0%)	85	(26.0%)
	Fever	17	(5.2%)	27	(8.2%)	18	(5.5%)
	Allergic Reaction	13	(4.0%)	25	(7.6%)	12	(3.7%)
Nervous System	Headache	20	(6.1%)	42	(12.8%)	48	(14.7%)
Respiratory System	Cough Increased	14	(4.3%)	21	(6.4%)	16	(4.9%)
	Asthma	8	(2.4%)	16	(4.9%)	18	(5.5%)
Skin & Appendages	Pruritus	96	(29.3%)	141	(43.0%)	128	(39.1%)
	Skin Burning	77	(23.5%)	143	(43.6%)	156	(47.7%)
	Skin Erythema	51	(15.5%)	64	(19.5%)	74	(22.6%)
	Skin Infection	27	(8.2%)	32	(9.8%)	18	(5.5%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group.
A patient could have had more than one adverse event.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.1).

Reviewer's Comments:

For the label, all adverse events (AE) occurring in 1% or more of the treated patients should be included. This information may be obtained from the NDA, ISS, Appendix 8.4.13.6.1.1.

Interestingly, the list of these AE includes contact dermatitis occurring in 0.9%, 2.4% and 1.5% of patients treated with the vehicle, 0.03% and 0.1% Tacrolimus formulations, respectively. This supports the previous conclusion of the reviewer regarding the contact sensitizing potential of the Tacrolimus formulation (see section 8.2.2 of this review).

8.5.1.2.2 Adverse Events by Population Subset

8.5.1.2.2.1 Adverse Events By Age

The incidence of treatment emergent adverse events in the three pivotal studies is presented by age in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.1).

In general, the overall incidence of adverse events was generally somewhat higher among younger children (2-6 years of age) than older children (7-15 years of age) in all three treatment groups. This is not unexpected given that this age group is undergoing *first exposure* to other children. The overall incidence for individual age groupings of children 2, 3, 4, 5, and 6 years of age were comparable to that for the group of younger children (2-6 years of age) as a whole.

The overall incidence of treatment emergent adverse events is presented by age in Table 48.

Table 48: Summary of the Overall Raw Incidence of Adverse Events By Age: Three Pivotal Studies

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Pediatric 2-15 years of age†	87/116 (75.0%)	99/118 (83.9%)	91/118 (77.1%)
2-6 years of age	57/72 (79.2%)	64/74 (86.5%)	57/69 (82.6%)
2 years of age	*18/21 (85.7%)*	*14/17 (82.4%)*	*15/17 (88.2%)*
3 years of age	*15/18 (83.3%)*	*20/22 (90.9%)*	*13/17 (76.5%)*
4 years of age	*10/14 (71.4%)*	*13/15 (86.7%)*	*12/13 (92.3%)*
5 years of age	*6/8 (75.0%)*	*11/11 (100.0%)*	*8/11 (72.7%)*
6 years of age	*8/11 (72.7%)*	*6/9 (66.7%)*	*9/11 (81.8%)*
7-15 years of age†	30/44 (68.2%)	35/44 (79.5%)	34/49 (69.4%)
Adult ≥16 years of age	152/212 (71.7%)	187/210 (89.0%)	183/209 (87.6%)
16-64 years of age	146/202 (72.3%)	179/201 (89.1%)	171/197 (86.8%)
≥65 years of age	6/10 (60.0%)	8/9 (88.9%)	12/12 (100.0%)

Patient population: all randomized patients who received at least one dose of study drug.
† Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.1).

There were some age-related differences in the incidence of individual adverse events (see Tables 49, 50 described later). For example, the individual adverse events of fever and increased cough were more common among pediatric patients than adult patients in both the vehicle and the

tacrolimus ointment treatment groups, while the incidence of headache, alcohol intolerance, and erythema tended to be greater among adult patients. Among pediatric patients, there was a higher incidence of flu-like symptoms, increased cough, fever, and otitis media for younger children (2-6 years of age) than older children (7-15 years of age) in all three treatment groups; this is not unexpected since this is the age group undergoing *first exposure* to other children.

Since age differences in the incidence of individual adverse events were observed in all treatment groups, including vehicle, tacrolimus ointment does not appear to be associated with any age-related/selective effect, except that the incidence of skin burning and pruritus tended to be higher in older children and adults compared with younger children in the 0.1% tacrolimus ointment group.

The incidence of common adverse events for pediatric patients (2-15 years of age) and adult patients (≥16 years of age) is presented in Table 49. The incidence of common adverse events for pediatric patients (2-6 years of age and 7-15 years of age) is presented in Table 50.

Table 49: Summary of the Raw Incidence of Individual Adverse Events† By Age: Three Pivotal Studies, Pediatric and Adult Patients

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Pediatric Patients (2-15 years of age)‡		***N=116***	***N=118***	***N=118***
Body As a Whole	Flu Syndrome	19 (16.4%)	28 (23.7%)	33 (28.0%)
	Fever	12 (10.3%)	21 (17.8%)	17 (14.4%)
	Allergic Reaction	5 (4.3%)	4 (3.4%)	3 (2.5%)
Nervous System Headache		5 (4.3%)	5 (4.2%)	13 (11.0%)
Respiratory System	Cough Increased	12 (10.3%)	19 (16.1%)	15 (12.7%)
	Asthma	5 (4.3%)	6 (5.1%)	11 (9.3%)
Skin & Appendages	Pruritus	26 (22.4%)	47 (39.8%)	36 (30.5%)
	Skin Burning	30 (25.9%)	49 (41.5%)	39 (33.1%)
	Skin Erythema	13 (11.2%)	14 (11.9%)	18 (15.3%)
	Skin Infection	11 (9.5%)	10 (8.5%)	10 (8.5%)
Adult Patients (≥16 years of age)		***N=212***	***N=210***	***N=209***
Body As a Whole	Flu Syndrome	22 (10.4%)	41 (19.5%)	52 (24.9%)
	Fever	5 (2.4%)	6 (2.9%)	1 (0.5%)
	Allergic Reaction	8 (3.8%)	21 (10.0%)	9 (4.3%)
Nervous System Headache		15 (7.1%)	37 (17.6%)	35 (16.7%)
Respiratory System	Cough Increased	2 (0.9%)	2 (1.0%)	1 (0.5%)
	Asthma	3 (1.4%)	10 (4.8%)	7 (3.3%)
Skin & Appendages	Pruritus	70 (33.0%)	94 (44.8%)	92 (44.0%)
	Skin Burning	47 (22.2%)	94 (44.8%)	117 (56.0%)
	Skin Erythema	38 (17.9%)	50 (23.8%)	56 (26.8%)
	Skin Infection	16 (7.5%)	22 (10.5%)	8 (3.8%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of age as shown in Table . A patient could have had more than one adverse event.
‡ Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.1).

Table 50: Summary of the Raw Incidence of Individual Adverse Events† By Age: Three Pivotal Studies, Pediatric Patients

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Pediatric Patients (2-6 years of age)		*N=72*	*N=74*	*N=69*
Body As a Whole	Flu Syndrome	13 (18.1%)	21 (28.4%)	25 (36.2%)
	Fever	10 (13.9%)	17 (23.0%)	14 (20.3%)
	Allergic Reaction	4 (5.6%)	2 (2.7%)	1 (1.4%)
Nervous System	Headache	3 (4.2%)	2 (2.7%)	4 (5.8%)
Respiratory System	Cough Increased	8 (11.1%)	13 (17.6%)	11 (15.9%)
	Asthma	2 (2.8%)	5 (6.8%)	4 (5.8%)
Skin & Appendages	Pruritus	16 (22.2%)	34 (45.9%)	19 (27.5%)
	Skin Burning	21 (29.2%)	29 (39.2%)	19 (27.5%)
	Skin Erythema	9 (12.5%)	9 (12.2%)	9 (13.0%)
	Skin Infection	7 (9.7%)	7 (9.5%)	6 (8.7%)
Pediatric Patients (7-15 years of age)‡		*N=44*	*N=44*	*N=49*
Body As a Whole	Flu Syndrome	6 (13.6%)	7 (15.9%)	8 (16.3%)
	Fever	2 (4.5%)	4 (9.1%)	3 (6.1%)
	Allergic Reaction	1 (2.3%)	2 (4.5%)	2 (4.1%)
Nervous System	Headache	2 (4.5%)	3 (6.8%)	9 (18.4%)
Respiratory System	Cough Increased	4 (9.1%)	6 (13.6%)	4 (8.2%)
	Asthma	3 (6.8%)	1 (2.3%)	7 (14.3%)
Skin & Appendages	Pruritus	10 (22.7%)	13 (29.5%)	17 (34.7%)
	Skin Burning	9 (20.5%)	20 (45.5%)	20 (40.8%)
	Skin Erythema	4 (9.1%)	5 (11.4%)	9 (18.4%)
	Skin Infection	4 (9.1%)	3 (6.8%)	4 (8.2%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of age as shown in Table . A patient could have had more than one adverse event.
‡ Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.1).

8.5.1.2.2.2 Adverse Events By Gender

The incidence of treatment emergent adverse events in the three pivotal studies is presented by gender in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.2).

Generally, the adverse event profile observed was similar between male and female patients, although headache and the sensation of skin burning tended to have a somewhat greater incidence among female patients in all three treatment groups. Tacrolimus ointment does not

appear to be associated with any gender-related/selective effect. The incidence of common adverse events by gender is presented in Table 51.

Table 51: Summary of the Raw Incidence of Individual Adverse Events† By Gender: Three Pivotal Studies

		Treatment Group					
		Vehicle		Concentration of Tacrolimus Ointment			
				0.03%		0.1%	
Males		*N=148*		*N=150*		*N=142*	
Overall Adverse Event Incidence		102	(68.9%)	129	(86.0%)	116	(81.7%)
Body As a Whole	Flu Syndrome	15	(10.1%)	35	(23.3%)	33	(23.2%)
	Fever	10	(6.8%)	11	(7.3%)	9	(6.3%)
	Allergic Reaction	6	(4.1%)	9	(6.0%)	6	(4.2%)
Nervous System	Headache	5	(3.4%)	14	(9.3%)	14	(9.9%)
Respiratory System	Cough Increased	8	(5.4%)	10	(6.7%)	6	(4.2%)
	Asthma	2	(1.4%)	5	(3.3%)	7	(4.9%)
Skin & Appendages	Pruritus	39	(26.4%)	59	(39.3%)	53	(37.3%)
	Skin Burning	29	(19.6%)	61	(40.7%)	60	(42.3%)
	Skin Erythema	22	(14.9%)	31	(20.7%)	30	(21.1%)
	Skin Infection	11	(7.4%)	16	(10.7%)	12	(8.5%)
Females		*N=180*		*N=178*		*N=185*	
Overall Adverse Event Incidence		137	(76.1%)	157	(88.2%)	158	(85.4%)
Body As a Whole	Flu Syndrome	26	(14.4%)	34	(19.1%)	52	(28.1%)
	Fever	7	(3.9%)	16	(9.0%)	9	(4.9%)
	Allergic Reaction	7	(3.9%)	16	(9.0%)	6	(3.2%)
Nervous System	Headache	15	(8.3%)	28	(15.7%)	34	(18.4%)
Respiratory System	Cough Increased	6	(3.3%)	11	(6.2%)	10	(5.4%)
	Asthma	6	(3.3%)	11	(6.2%)	11	(5.9%)
Skin & Appendages	Pruritus	57	(31.7%)	82	(46.1%)	75	(40.5%)
	Skin Burning	48	(26.7%)	82	(46.1%)	96	(51.9%)
	Skin Erythema	29	(16.1%)	33	(18.5%)	44	(23.8%)
	Skin Infection	16	(8.9%)	16	(9.0%)	6	(3.2%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of gender as shown in Table .
A patient could have had more than one adverse event.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13. (ISS Statistical Appendix 8.4.13.6.1.3.2).

8.5.1.2.2.3 Adverse Events By Race

The incidence of treatment emergent adverse events in the three pivotal studies is presented by race in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.3).

Differences in the incidence of adverse events among races (White, Black, Oriental) were observed in both the vehicle and tacrolimus ointment treatment groups. In general, blacks tended to have a lower incidence of adverse events than whites (see Table 52 described later). For example, the incidence of skin erythema was noticeably lower in all treatment groups for blacks compared with whites (although this may be a pigmentation-related detection effect). Furthermore, hyperesthesia was noted in 16 white tacrolimus ointment-treated patients (2.5% of all white patients; 3.7% of white tacrolimus ointment-treated patients) and only 1 black vehicle patient (0.4% of all black patients; 1.2% of black vehicle-treated patients). Also, alcohol intolerance was noted in 17 white tacrolimus ointment-treated patients (2.6% of all white patients; 3.9% of white tacrolimus ointment-treated patients) and not in any black patients; again this may be a pigmentation-related detection effect. The incidence of skin burning was also higher in white patients compared with black patients.

The incidence of common adverse events by race is presented in Table 52.

Table 52: Summary of the Raw Incidence of Individual Adverse Events† By Race: Three Pivotal Studies

		Treatment Group					
		Vehicle		Concentration of Tacrolimus Ointment			
				0.03%		0.1%	
White		***N=218***		***N=220***		***N=214***	
Overall Adverse Event Incidence		162	(74.3%)	197	(89.5%)	191	(89.3%)
Body As a Whole	Flu Syndrome	23	(10.6%)	57	(25.9%)	57	(26.6%)
	Fever	13	(6.0%)	18	(8.2%)	13	(6.1%)
	Allergic Reaction	10	(4.6%)	20	(9.1%)	9	(4.2%)
Nervous System	Headache	13	(6.0%)	30	(13.6%)	41	(19.2%)
Respiratory System	Cough Increased	11	(5.0%)	16	(7.3%)	11	(5.1%)
	Asthma	5	(2.3%)	11	(5.0%)	17	(7.9%)
Skin & Appendages	Pruritus	67	(30.7%)	98	(44.5%)	95	(44.4%)
	Skin Burning	52	(23.9%)	102	(46.4%)	112	(52.3%)
	Skin Erythema	43	(19.7%)	47	(21.4%)	60	(28.0%)
	Skin Infection	19	(8.7%)	25	(11.4%)	13	(6.1%)
Black		***N=85***		***N=87***		***N=89***	
Overall Adverse Event Incidence		59	(69.4%)	70	(80.5%)	60	(67.4%)
Body As a Whole	Flu Syndrome	12	(14.1%)	8	(9.2%)	19	(21.3%)
	Fever	2	(2.4%)	5	(5.7%)	3	(3.4%)
	Allergic Reaction	3	(3.5%)	5	(5.7%)	3	(3.4%)
Nervous System	Headache	4	(4.7%)	9	(10.3%)	6	(6.7%)
Respiratory System	Cough Increased	2	(2.4%)	3	(3.4%)	3	(3.4%)
	Asthma	2	(2.4%)	2	(2.3%)	0	
Skin & Appendages	Pruritus	23	(27.1%)	36	(41.4%)	26	(29.2%)
	Skin Burning	19	(22.4%)	31	(35.6%)	30	(33.7%)
	Skin Erythema	4	(4.7%)	13	(14.9%)	11	(12.4%)
	Skin Infection	5	(5.9%)	5	(5.7%)	2	(2.2%)

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(Table continued)

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Oriental		***N=18***	***N=16***	***N=18***
Overall Adverse Event Incidence		13 (72.2%)	15 (93.8%)	18 (100.0%)
Body As a Whole	Flu Syndrome	5 (27.8%)	3 (18.8%)	8 (44.4%)
	Fever	2 (11.1%)	2 (12.5%)	2 (11.1%)
	Allergic Reaction	0	0	0
Nervous System	Headache	2 (11.1%)	0	0
Respiratory System	Cough Increased	1 (5.6%)	2 (12.5%)	2 (11.1%)
	Asthma	1 (5.6%)	0	1 (5.6%)
Skin & Appendages	Pruritus	3 (16.7%)	5 (31.3%)	4 (22.2%)
	Skin Burning	5 (27.8%)	7 (43.8%)	10 (55.6%)
	Skin Erythema	3 (16.7%)	3 (18.8%)	2 (11.1%)
	Skin Infection	2 (11.1%)	2 (12.5%)	1 (5.6%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of race as shown in Table .
A patient could have had more than one adverse event.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13. (ISS Statistical Appendix 8.4.13.6.1.3.3).

8.5.1.2.2.4 Adverse Events By Baseline Disease Severity (Moderate, Severe)

The incidence of treatment emergent adverse events in the three pivotal studies is presented by baseline disease severity in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.4).

In both tacrolimus ointment treatment groups (but not vehicle), there was a greater incidence of the sensation of skin burning, skin erythema, and skin infection among patients with severe atopic dermatitis at baseline compared to those with moderate disease. It is not unexpected that patients with more significant skin disruption would be more susceptible to these events. The incidence of common adverse events by baseline disease severity is presented in Table 53.

Table 53: Summary of the Raw Incidence of Individual Adverse Events† By Baseline Disease Severity: Three Pivotal Studies

		Treatment Group					
		Vehicle		Concentration of Tacrolimus Ointment			
				0.03%		0.1%	
Moderate Disease at Baseline		***N=145***		***N=138***		***N=129***	
Overall Adverse Event Incidence		117	(80.7%)	120	(87.0%)	106	(82.2%)
Body As a Whole	Flu Syndrome	26	(17.9%)	33	(23.9%)	31	(24.0%)
	Fever	7	(4.8%)	9	(6.5%)	7	(5.4%)
	Allergic Reaction	7	(4.8%)	10	(7.2%)	2	(1.6%)
Nervous System	Headache	16	(11.0%)	22	(15.9%)	22	(17.1%)
Respiratory System	Cough Increased	8	(5.5%)	9	(6.5%)	9	(7.0%)
	Asthma	3	(2.1%)	6	(4.3%)	4	(3.1%)
Skin & Appendages	Pruritus	45	(31.0%)	58	(42.0%)	45	(34.9%)
	Skin Burning	34	(23.4%)	44	(31.9%)	56	(43.4%)
	Skin Erythema	21	(14.5%)	18	(13.0%)	23	(17.8%)
	Skin Infection	10	(6.9%)	7	(5.1%)	3	(2.3%)
Severe Disease at Baseline		***N=183***		***N=190***		***N=198***	
Overall Adverse Event Incidence		122	(66.7%)	166	(87.4%)	168	(84.8%)
Body As a Whole	Flu Syndrome	15	(8.2%)	36	(18.9%)	54	(27.3%)
	Fever	10	(5.5%)	18	(9.5%)	11	(5.6%)
	Allergic Reaction	6	(3.3%)	15	(7.9%)	10	(5.1%)
Nervous System	Headache	4	(2.2%)	20	(10.5%)	26	(13.1%)
Respiratory System	Cough Increased	6	(3.3%)	12	(6.3%)	7	(3.5%)
	Asthma	5	(2.7%)	10	(5.3%)	14	(7.1%)
Skin & Appendages	Pruritus	51	(27.9%)	83	(43.7%)	83	(41.9%)
	Skin Burning	43	(23.5%)	99	(52.1%)	100	(50.5%)
	Skin Erythema	30	(16.4%)	46	(24.2%)	51	(25.8%)
	Skin Infection	17	(9.3%)	25	(13.2%)	15	(7.6%)

Patient population: all randomized patients who received at least one dose of study drug.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of baseline disease severity as shown in Table .
A patient could have had more than one adverse event.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.4).

8.5.1.2.2.5 Adverse Events By Percent Affected BSA

The incidence of treatment emergent adverse events in the three pivotal studies is presented by percent affected body surface area (BSA) at baseline the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.5).

In all treatment groups, including vehicle, the incidence of skin infection tended to increase with increasing body surface area involvement at baseline, which might be anticipated in view of the

extent of disruption of the protective barrier of the skin. In addition, the incidence of skin burning, skin erythema, and folliculitis was highest for tacrolimus ointment-treated patients with >75% of their body surface area affected at baseline. The incidence of common adverse events by percent BSA affected at baseline is presented in Table 54.

Table 54: Summary of the Raw Incidence of Individual Adverse Events† By Percent BSA Affected at Baseline: Three Pivotal Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
10%-25%		*N=95*	*N=107*	*N=92*
Overall Adverse Event Incidence		74 (77.9%)	90 (84.1%)	73 (79.3%)
Body As a Whole	Flu Syndrome	16 (16.8%)	24 (22.4%)	19 (20.7%)
	Fever	6 (6.3%)	9 (8.4%)	5 (5.4%)
	Allergic Reaction	5 (5.3%)	8 (7.5%)	0
Nervous System	Headache	12 (12.6%)	15 (14.0%)	19 (20.7%)
Respiratory System	Cough Increased	6 (6.3%)	9 (8.4%)	7 (7.6%)
	Asthma	1 (1.1%)	6 (5.6%)	5 (5.4%)
Skin & Appendages	Pruritus	29 (30.5%)	45 (42.1%)	35 (38.0%)
	Skin Burning	20 (21.1%)	38 (35.5%)	40 (43.5%)
	Skin Erythema	12 (12.6%)	9 (8.4%)	20 (21.7%)
	Skin Infection	4 (4.2%)	4 (3.7%)	1 (1.1%)
>25%-50%		*N=98*	*N=91*	*N=98*
Overall Adverse Event Incidence		70 (71.4%)	78 (85.7%)	84 (85.7%)
Body As a Whole	Flu Syndrome	10 (10.2%)	18 (19.8%)	23 (23.5%)
	Fever	5 (5.1%)	5 (5.5%)	5 (5.1%)
	Allergic Reaction	4 (4.1%)	9 (9.9%)	3 (3.1%)
Nervous System	Headache	4 (4.1%)	13 (14.3%)	9 (9.2%)
Respiratory System	Cough Increased	4 (4.1%)	5 (5.5%)	5 (5.1%)
	Asthma	1 (1.0%)	4 (4.4%)	4 (4.1%)
Skin & Appendages	Pruritus	27 (27.6%)	36 (39.6%)	37 (37.8%)
	Skin Burning	26 (26.5%)	42 (46.2%)	42 (42.9%)
	Skin Erythema	22 (22.4%)	19 (20.9%)	21 (21.4%)
	Skin Infection	8 (8.2%)	9 (9.9%)	5 (5.1%)

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(Table continued)

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
>50%-75%		*N=66*	*N=70*	*N=73*
Overall Adverse Event Incidence		51 (77.3%)	62 (88.6%)	62 (84.9%)
Body As a Whole	Flu Syndrome	7 (10.6%)	15 (21.4%)	25 (34.2%)
	Fever	0	9 (12.9%)	3 (4.1%)
	Allergic Reaction	1 (1.5%)	6 (8.6%)	2 (2.7%)
Nervous System	Headache	2 (3.0%)	4 (5.7%)	7 (9.6%)
Respiratory System	Cough Increased	0	3 (4.3%)	1 (1.4%)
	Asthma	5 (7.6%)	2 (2.9%)	6 (8.2%)
Skin & Appendages	Pruritus	23 (34.8%)	29 (41.4%)	35 (47.9%)
	Skin Burning	13 (19.7%)	30 (42.9%)	36 (49.3%)
	Skin Erythema	10 (15.2%)	13 (18.6%)	14 (19.2%)
	Skin Infection	9 (13.6%)	8 (11.4%)	6 (8.2%)
>75% - 100%		*N=69*	*N=60*	*N=64*
Overall Adverse Event Incidence		44 (63.8%)	56 (93.3%)	55 (85.9%)
Body As a Whole	Flu Syndrome	8 (11.6%)	12 (20.0%)	18 (28.1%)
	Fever	6 (8.7%)	4 (6.7%)	5 (7.8%)
	Allergic Reaction	3 (4.3%)	2 (3.3%)	7 (10.9%)
Nervous System	Headache	2 (2.9%)	10 (16.7%)	13 (20.3%)
Respiratory System	Cough Increased	4 (5.8%)	4 (6.7%)	3 (4.7%)
	Asthma	1 (1.4%)	4 (6.7%)	3 (4.7%)
Skin & Appendages	Pruritus	17 (24.6%)	31 (51.7%)	21 (32.8%)
	Skin Burning	18 (26.1%)	33 (55.0%)	38 (59.4%)
	Skin Erythema	7 (10.1%)	23 (38.3%)	19 (29.7%)
	Skin Infection	6 (8.7%)	11 (18.3%)	6 (9.4%)

Patient population: all randomized patients who received at least one dose of study drug.
BSA: body surface area.
† Adverse events experienced by at least 5% of patients in any treatment group regardless of percent BSA affected at baseline as shown in Table .
A patient could have had more than one adverse event.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.3.5).

8.5.1.2.3 Drug-Related Adverse Events

Adverse events were assigned a relationship (possibly, probably, or none) to study drug by the investigator before the blind was broken. The incidence of drug-related adverse events in the three pivotal studies is presented in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.2.1 and 8.4.13.6.2.2).

Most of the adverse events that were considered to be drug-related were application site adverse events. The more common drug-related adverse events in the three studies combined, as well as in adult patients and pediatric patients, were pruritus, the sensation of skin burning, and skin erythema.

8.5.1.2.4 Application Site and Nonapplication site Adverse Events

Adverse events were categorized as application site events or nonapplication site events at the time of data collection. The incidence of application site adverse events in the three pivotal studies is presented in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.3.1 and 8.4.13.6.3.2) and the incidence of nonapplication site adverse events is presented in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.4.1 and 8.4.13.6.4.2). Refer also to the individual study reports (Studies 97-0-037, 97-0-035, 97-0-036).

The more common application site adverse events in the three studies combined were the sensation of skin burning, pruritus, and skin erythema. In each study, for the majority of patients with an application site adverse event in all three treatment groups, the intensity of the worst episode was mild or moderate. The incidence of head/neck application site adverse events was not higher than the incidence for other body regions for all treatment groups. The prevalence of skin burning, pruritus, and erythema was highest for all treatment groups in the pediatric and adult studies during ~~the~~ first 4 days of treatment and declined thereafter. Each episode of these events was short-lived, generally lasting 2 hours or less. Generally, these events tended to be mild or moderate in severity and rarely resulted in discontinuation of treatment (<2% pediatric patients, <5% adults) (Table 13.1.2, Studies 97-0-037, 97-0-035, and 97-0-036).

The more common nonapplication site adverse events in the three studies combined were flu-like symptoms and headache. For most patients with a nonapplication site adverse event in each pivotal study, the intensity of the worst episode was mild or moderate.

Reviewer's Comments:

The analysis of the results in this section, 8.5.1.2, shows interesting differences in certain groups of AE and in certain sub-populations. However, it seems none of these differences is of sufficient clinical significance or safety concern to necessitate its inclusion in the label without making it unnecessarily to. elaborate and more difficult to read.

8.5.1.3 Adjusted 12-Week Adverse Events

A total of 64% of patients in the vehicle treatment group prematurely discontinued treatment in the study, primarily due to lack of efficacy (Section 8.3.3.2, ISE); this resulted in fewer treatment days for the vehicle group (median = 25.5 days) compared with the tacrolimus ointment treatment groups (median = 84 days, 0.03% and 85 days, 0.1%) (see NDA, ISS, Section 8.4.13, ISS Statistical Appendix 8.4.13.3.1). Therefore, Kaplan-Meier analyses that adjusted for treatment days were performed. The adjusted incidence rate represents the expected incidence over 12 weeks. The adjusted incidence rate is the basis of statistical inferences with respect to the comparisons of adverse event incidence.

8.5.1.3.1 Overall Adjusted 12-Week Adverse Events Incidence Rate

The results of adjusted 12-week incidence rate analyses for patients in the three studies combined are shown in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.1.2.1, 8.4.13.6.1.2.2, and 8.4.13.6.1.2.3).

The adjusted incidence rates of overall infections and nonapplication site adverse events were similar between both tacrolimus ointment groups and vehicle. The adjusted 12-week incidence rate of adverse events resulting in discontinuation was significantly lower in the tacrolimus ointment groups compared with vehicle. Overall application site and drug-related adverse events had a significantly higher adjusted incidence rate in both tacrolimus ointment groups compared with vehicle; the differences were primarily due to a higher incidence of skin burning and pruritus, events that were generally mild or moderate in severity and of limited duration. A summary of the adjusted 12-week incidence rates of adverse events occurring during the treatment period (treatment emergent) for the three pivotal studies combined is presented Table 55. Individual events with a statistically significant treatment difference in adjusted 12-week incidence rate are summarized in Table 56.

Table 55: Summary of the Adjusted 12-Week Incidence Rate of Treatment Emergent Adverse Events: Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle N=328	0.03% N=328	0.1% N=327	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	Rate ± Standard Error‡						
Overall AE	83.9 ± 2.63	89.8 ± 1.79	88.5 ± 1.97	5.9 (-0.4, 12.1)	4.6 (-1.8, 11.1)	0.065	0.158
Overall Drug-Related AE	56.1 ± 3.08	72.4 ± 2.54	68.3 ± 2.66	16.4 (8.5, 24.2)	12.2 (4.2, 20.2)	<0.001	0.003
Application Site AE	59.5 ± 3.06	75.2 ± 2.47	72.4 ± 2.58	15.7 (8.0, 23.4)	12.8 (5.0, 20.6)	<0.001	0.001
Nonapplication Site AE	68.3 ± 3.74	69.7 ± 2.88	67.5 ± 2.89	1.4 (-7.9, 10.7)	-0.7 (-10.0, 8.5)	0.766	0.880
Infections	54.3 ± 3.91	56.4 ± 3.05	57.5 ± 3.13	2.1 (-7.6, 11.8)	3.2 (-6.6, 13.0)	0.670	0.522
AE Resulting in Discontinuation	13.1 ± 2.17	6.9 ± 1.52	5.2 ± 1.27	-6.2 (-11.4, -1.0)	-7.9 (-12.8, -3.0)	0.019	0.002

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval. AE: adverse event. § From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12. Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.1).

Table 56: Summary of the Adjusted 12-Week Incidence Rate of Individual Adverse Events†: Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle N=328	0.03% N=328	0.1% N=327	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	Rate ± Standard Error‡						
Acne	1.4 ± 0.84	2.7 ± 0.95	4.8 ± 1.34	1.3 (-1.2, 3.8)	3.4 (0.3, 6.5)	0.300	0.030
Alcohol Intolerance	0.0 ± 0.00	2.1 ± 0.87	4.3 ± 1.21	2.1 (0.4, 3.8)	4.3 (1.9, 6.7)	0.014	<0.001
Cyst	0.0 ± 0.00	0.7 ± 0.51	1.9 ± 0.95	0.7 (-0.3, 1.7)	1.9 (0.0, 3.8)	0.159	0.047
Dyspepsia	0.7 ± 0.47	0.7 ± 0.51	2.8 ± 0.98	0.1 (-1.3, 1.4)	2.2 (0.0, 4.3)	0.934	0.048
Flu Syndrome	21.8 ± 3.31	24.9 ± 2.67	31.2 ± 2.85	3.0 (-5.3, 11.4)	9.3 (0.8, 17.9)	0.476	0.033
Folliculitis	0.3 ± 0.33	4.7 ± 1.23	3.0 ± 1.00	4.4 (1.9, 6.9)	2.7 (0.6, 4.8)	0.001	0.010
Headache	9.9 ± 2.32	14.4 ± 2.07	16.5 ± 2.21	4.5 (-1.6, 10.6)	6.6 (0.3, 12.9)	0.152	0.040
Herpes Zoster	0.0 ± 0.00	2.3 ± 1.02	0.4 ± 0.40	2.3 (0.3, 4.3)	0.4 (-0.4, 1.2)	0.026	0.316
Hyperesthesia	0.3 ± 0.30	1.9 ± 0.77	4.1 ± 1.11	1.6 (0.0, 3.2)	3.8 (1.5, 6.1)	0.054	0.001
Myalgia	0.0 ± 0.00	1.8 ± 0.80	1.4 ± 0.71	1.8 (0.2, 3.4)	1.4 (0.0, 2.8)	0.026	0.046
Pruritus	33.1 ± 3.01	44.3 ± 2.82	41.1 ± 2.84	11.2 (3.1, 19.3)	8.0 (-0.1, 16.1)	0.007	0.054
Skin Burning	27.0 ± 2.79	44.7 ± 2.81	49.0 ± 2.83	17.6 (9.9, 25.4)	21.9 (14.1, 29.7)	<0.001	<0.001
Skin Tingling	1.9 ± 0.79	2.8 ± 0.92	4.8 ± 1.22	0.9 (-1.5, 3.2)	2.9 (0.0, 5.7)	0.482	0.048

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval. † Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle. § From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12. Alcohol intolerance = skin/facial flushing, redness, heat sensation, etc. Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc. Folliculitis = swollen or infected hair follicle. Hyperesthesia = generally localized, hypersensitive reaction, sensitive skin, skin sensitive to temperature changes, etc. Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.2).

8.5.1.3.2 Adjusted 12-Week Incidence Rate of Adverse Events: Pediatric Patients

The results of the adjusted 12-week incidence rate analyses for pediatric patients in the three pivotal studies are shown in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3). Adjusted 12-week incidence rates for those individual events with a statistically

significant difference between either tacrolimus ointment treatment group and vehicle are presented in Table 57.

Table 57: Summary of the Adjusted 12-Week Incidence Rate of Individual Adverse Events†: Pediatric Patients (2-15 Years of Age) in the Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle N=116	0.03% N=118	0.1% N=118	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	Rate ± Standard Error‡						
Herpes Zoster	0.0 ± 0.00	4.8 ± 2.36	1.1 ± 1.06	4.8 (0.2, 9.4)	1.1 (-1.0, 3.1)	0.042	0.315
Pruritus	26.6 ± 4.90	41.2 ± 4.65	32.2 ± 4.51	14.6 (1.4, 27.9)	5.7 (-7.4, 18.7)	0.030	0.394
Sinusitis	8.0 ± 3.34	3.3 ± 1.90	1.0 ± 1.04	-4.7 (-12.2, 2.8)	-7.0 (-13.9, -0.1)	0.221	0.046
Skin Burning	29.0 ± 4.74	42.7 ± 4.67	33.7 ± 4.42	13.7 (0.6, 26.7)	4.7 (-8.0, 17.4)	0.040	0.467
Vesiculobullous Rash	0.0 ± 0.00	3.8 ± 1.85	1.0 ± 0.99	3.8 (0.1, 7.4)	1.0 (-0.9, 2.9)	0.042	0.315

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval. Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.

† Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle.

§ From Normal Approximation test based on Kaplan-Meier Estimates. Statistical significance is indicated by p-values ≤0.05.

‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.

Skin burning = burning sensation, pain, stinging, soreness, etc.

Herpes zoster = five cases of *chicken pox*.

Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).

Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3).

In pediatric patients (2-15 years of age), the individual events with a statistically significant difference between the 0.03% tacrolimus ointment group and vehicle were local irritation events (sensation of skin burning and pruritus) and the low-incidence events, vesiculobullous rash and herpes zoster. All five cases of herpes zoster were *chicken pox* in children ≤8 years of age who had a normal clinical course (Study 97-0-037, Section 9.1.3). No event occurred at a statistically higher rate compared with vehicle in the 0.1% tacrolimus ointment group. Sinusitis had a statistically lower adjusted incidence rate in the 0.1% tacrolimus ointment group compared with vehicle.

Reviewer's Comments:

The sponsor used the "Costart" term "Herpes Zoster" to include both kinds of diseases caused by Varicella Zoster Virus, i.e. Chicken Pox which is a new infection with HZV common in

unvaccinated children, and Herpes Zoster which is a reactivation of latent HZV infection in adults. The latter is usually associated with decreased immunity.

8.5.1.3.3 Adjusted 12-Week Incidence Rate of Adverse Events: Adult Patients

The results of the adjusted incidence rate analyses for adult patients in the three pivotal studies are shown in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3). Adjusted 12-week incidence rates for those individual events with a statistically significant difference between either tacrolimus ointment treatment group and vehicle are presented in Table 58.

Table 58: Summary of the Adjusted 12-Week Incidence Rate of Individual Adverse Events†: Adult Patients (≥16 Years of Age) in the Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle	0.03%	0.1%	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	N=212	N=210	N=209				
	Rate ± Standard Error‡						
Acne	1.8 ± 1.30	4.3 ± 1.48	7.1 ± 2.02	2.5 (-1.4, 6.3)	5.3 (0.6, 10.0)	0.213	0.028
Alcohol Intolerance	0.0 ± 0.00	3.4 ± 1.36	6.9 ± 1.92	3.4 (0.7, 6.0)	6.9 (3.1, 10.7)	0.013	<0.001
Back Pain	0.0 ± 0.00	2.3 ± 1.16	1.6 ± 0.92	2.3 (0.0, 4.6)	1.6 (-0.2, 3.4)	0.046	0.081
Cyst	0.0 ± 0.00	1.1 ± 0.81	3.1 ± 1.55	1.1 (-0.4, 2.7)	3.1 (0.1, 6.1)	0.159	0.046
Flu Syndrome	19.3 ± 4.06	23.2 ± 3.28	30.8 ± 3.61	3.9 (-6.3, 14.2)	11.5 (0.9, 22.2)	0.451	0.034
Folliculitis	0.5 ± 0.51	6.2 ± 1.74	4.3 ± 1.50	5.7 (2.1, 9.3)	3.8 (0.7, 6.9)	0.002	0.016
Headache	10.7 ± 2.79	20.0 ± 2.99	19.2 ± 2.99	9.3 (1.3, 17.4)	8.6 (0.6, 16.6)	0.022	0.036
Hyperesthesia	0.5 ± 0.47	3.0 ± 1.19	6.5 ± 1.74	2.5 (0.0, 5.0)	6.0 (2.5, 9.5)	0.052	0.001
Myalgia	0.0 ± 0.00	2.8 ± 1.28	1.6 ± 0.91	2.8 (0.3, 5.4)	1.6 (-0.2, 3.4)	0.026	0.081
Rash	0.5 ± 0.50	4.9 ± 1.77	2.1 ± 1.27	4.4 (0.8, 8.0)	1.6 (-1.0, 4.3)	0.017	0.230
Sinusitis	0.7 ± 0.68	3.9 ± 1.45	2.2 ± 1.09	3.2 (0.0, 6.3)	1.5 (-1.0, 4.0)	0.048	0.241
Skin Burning	25.8 ± 3.43	45.6 ± 3.50	57.7 ± 3.52	19.8 (10.2, 29.4)	31.8 (22.2, 41.5)	<0.001	<0.001
Skin Tingling	2.4 ± 1.04	3.4 ± 1.27	7.6 ± 1.91	1.1 (-2.2, 4.3)	5.3 (1.0, 9.5)	0.522	0.015

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval. Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age. † Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle. § From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.

Alcohol intolerance = skin/facial flushing, redness, heat sensation, etc. Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc. Hyperesthesia = generally localized, hypersensitive reaction, sensitive skin, skin sensitive to temperature changes, etc. Skin burning = burning sensation, pain, stinging, soreness, etc Folliculitis = swollen or infected hair follicle.

Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).

Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3).

The adjusted 12-week incidence rates for adults were similar to those of the total population except that the rate of headache was also statistically significantly higher in the 0.03% tacrolimus ointment group compared with vehicle for adults and that a statistically significant treatment difference for rash, sinusitis, and back pain (higher in the 0.03% tacrolimus ointment group

compared with vehicle) was observed. Also, although significant for all patients, the adjusted incidence rates of pruritus, dyspepsia, and herpes zoster were not significantly different between either tacrolimus ointment group and vehicle for adults.

Reviewer's Comments:

The data in Tables 56, 57, and 58 include important information that should be conveyed to the prescribing physician. The reviewer has combined these 3 tables, simplified their presentation and assembled them in Table 59. It is recommended [redacted] the AE may be related to an effect of the active ingredient of the formulation.

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Table 59: Summary of the Adjusted 12-Week Incidence Rate of Individual Adverse Events[$]: Three Pivotal Studies

ADVERSE EVENT	Treatment Group			Stat. Significance[$]	
	Vehicle	0.03%	0.1%	0.03% vs Vehicle	0.1% vs Vehicle
	N=328	N=328	N=327		
	Rate				
Acne	1.4	2.7	4.8		***
Alcohol Intolerance	0.0	2.1	4.3	***	***
Back Pain	0.3	2.0	1.0	**	
Cyst	0.0	0.7	1.9		***
Dyspepsia	0.7	0.7	2.8		***
Flu Syndrome	21.8	24.9	31.2		***
Folliculitis	0.3	4.7	3.0	***	***
Headache	9.9	14.4	16.5	**	***
Varicella Zoster infection	0.0	2.3	0.4	***	
Hyperesthesia	0.3	1.9	4.1		***
Myalgia	0.0	1.8	1.4	***	***
Pruritus	33.1	44.3	41.1	***	
Rash	1.7	3.7	1.7	**	
Sinusitis	3.6	3.7	1.8	**	
Skin Burning	27.0	44.7	49.0	***	***
Skin Tingling	1.9	2.8	4.8		***
Vesiculobullous Rash	1.5	3.0	1.8	*	

$: This table includes all adverse events that had a statistically significant higher incidence in either the Tacrolimus 0.03% or 0.1% arm as compared to the vehicle arm in the 3 combined adult and pediatric 12-week controlled studies (***), the 2 combined adult studies only (**) or in the pediatric study only (*).

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8.5.1.3.4 Adjusted 12-Week Incidence Rate of Adverse Events: Infections

The raw incidence of infections in the three pivotal studies is presented in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.5.1 and 8.4.13.6.5.2). *Infection* was a predefined

cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc. (NDA, Reports on Studies 97-0-037, 97-0-035, and 97-0-036, Appendix 14.4.4.2).

There were no statistically significant treatment differences with respect to the overall adjusted 12-week incidence rate of infections (see NDA, ISS, Section 8.4.13, ISS Statistical Appendix 8.4.13.6.1.2.1). Individual infection adverse events which had a ≥5% adjusted 12-week incidence rate or demonstrated a statistically significant treatment difference in any treatment group are presented for the three studies combined in Table 60.

Table 60: Summary of the Adjusted 12-Week Incidence Rate of Individual Infections†: Three Pivotal Studies Combined

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle N=328	0.03% N=328	0.1% N=327	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	Rate ± Standard Error‡						
Cough Increased	6.9 ± 1.86	7.2 ± 1.53	6.2 ± 1.53	0.4 (-4.4, 5.1)	-0.7 (-5.4, 4.1)	0.883	0.783
Fever	7.7 ± 1.89	9.8 ± 1.82	6.9 ± 1.59	2.1 (-3.0, 7.2)	-0.8 (-5.7, 4.0)	0.425	0.735
Flu Syndrome	21.8 ± 3.31	24.9 ± 2.67	31.2 ± 2.85	3.0 (-5.3, 11.4)	9.3 (0.8, 17.9)	0.476	0.033
Folliculitis	0.3 ± 0.33	4.7 ± 1.23	3.0 ± 1.00	4.4 (1.9, 6.9)	2.7 (0.6, 4.8)	0.001	0.010
Herpes Zoster	0.0 ± 0.00	2.3 ± 1.02	0.4 ± 0.40	2.3 (0.3, 4.3)	0.4 (-0.4, 1.2)	0.026	0.316
Pharyngitis	6.1 ± 2.05	4.4 ± 1.24	5.1 ± 1.34	-1.7 (-6.4, 3.0)	-1.0 (-5.8, 3.8)	0.467	0.691
Skin Infection	11.8 ± 2.26	11.7 ± 1.97	7.1 ± 1.66	-0.1 (-6.0, 5.8)	-4.7 (-10.2, 0.8)	0.971	0.095

Patient population: all randomized patients who received at least one dose of study drug.
CI: confidence interval.
† Based on infection cluster (predefined cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc.). Includes those infections that had a 12-week adjusted incidence rate of ≥5% in any treatment group in the three pivotal studies combined, or demonstrated a statistically significant treatment difference.
§ From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05.
‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Folliculitis = swollen or infected hair follicle.
Herpes zoster = five cases of *chicken pox* and one case of *herpes zoster on upper lip*.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.2).

In all three studies combined, the adjusted 12-week incidence rate for folliculitis was significantly greater in both tacrolimus ointment treatment groups compared with vehicle. However, since cultures were not performed, it is not clear if all *folliculitis* events represented bacterial folliculitis. The adjusted incidence rate for flu syndrome was significantly greater than vehicle in the 0.1% tacrolimus ointment group, but not in the 0.03% tacrolimus ointment group.

Flu syndrome (*flu-like symptoms*) as reported in these studies may not entirely represent viral infection; non-specific *colds*, *stuffy nose*, etc. may be catarrh.

Individual infection adverse events which had an adjusted 12-week incidence rate ≥5% in any treatment group or demonstrated a statistically significant treatment difference for pediatric patients (2-15 years of age) in the three pivotal studies are presented in Table 61.

Table 61: Summary of the Adjusted 12-Week Incidence Rate of Individual Infections†: Pediatric Patients (2-15 Years of Age) in the Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle	0.03%	0.1%	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	N=116	N=118	N=118				
	Rate ± Standard Error‡						
Bronchitis	2.5 ± 1.80	3.0 ± 1.69	5.0 ± 2.21	0.5 (-4.4, 5.3)	2.6 (-3.0, 8.1)	0.848	0.370
Cough Increased	14.3 ± 3.96	17.9 ± 3.75	14.8 ± 3.55	3.7 (-7.0, 14.4)	0.5 (-9.9, 11.0)	0.501	0.921
Fever	13.4 ± 3.74	20.6 ± 4.05	17.1 ± 3.83	7.1 (-3.7, 17.9)	3.6 (-6.9, 14.1)	0.196	0.499
Flu Syndrome	25.4 ± 5.44	27.8 ± 4.55	31.8 ± 4.64	2.4 (-11.5, 16.3)	6.4 (-7.6, 20.4)	0.733	0.369
Herpes Zoster	0.0 ± 0.00	4.8 ± 2.36	1.1 ± 1.06	4.8 (0.2, 9.4)	1.1 (-1.0, 3.1)	0.042	0.315
Infection	8.7 ± 3.53	7.3 ± 2.67	3.7 ± 1.82	-1.5 (-10.1, 7.2)	-5.0 (-12.8, 2.7)	0.739	0.204
Otitis Media	5.6 ± 2.84	11.7 ± 3.36	9.2 ± 2.95	6.1 (-2.6, 14.7)	3.6 (-4.4, 11.6)	0.168	0.378
Pharyngitis	11.0 ± 4.33	6.0 ± 2.39	6.6 ± 2.41	-5.0 (-14.7, 4.6)	-4.5 (-14.2, 5.3)	0.308	0.369
Pustular Rash	3.0 ± 1.70	2.0 ± 1.37	6.1 ± 2.41	-1.0 (-5.3, 3.3)	3.1 (-2.7, 8.9)	0.644	0.294
Rhinitis	1.8 ± 1.29	5.7 ± 2.29	7.1 ± 2.60	3.9 (-1.2, 9.1)	5.3 (-0.4, 10.9)	0.136	0.070
Sinusitis	8.0 ± 3.34	3.3 ± 1.90	1.0 ± 1.04	-4.7 (-12.2, 2.8)	-7.0 (-13.9, -0.1)	0.221	0.046††
Skin Infection	13.5 ± 3.96	10.3 ± 3.10	11.0 ± 3.38	-3.3 (-13.1, 6.6)	-2.6 (-12.8, 7.6)	0.516	0.621

Patient population: all randomized patients who received at least one dose of study drug.
CI: confidence interval. Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
† Based on infection cluster (predefined cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc.). Includes those infections that had an adjusted 12-week incidence rate of ≥5% in any treatment group or demonstrated a statistically significant treatment difference for pediatric patients (2-15 years of age) in the three pivotal studies combined.
§ From Normal Approximation test based on Kaplan-Meier Estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
†† Incidence is significantly lower in the tacrolimus ointment group compared with vehicle.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Herpes zoster = five cases of *chicken pox*.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3).

For pediatric patients in the 0.1% tacrolimus ointment group, no infection event had a greater adjusted 12-week incidence rate compared with vehicle. The adjusted incidence rate of sinusitis was higher in the vehicle group compared with the 0.1% tacrolimus ointment group. Herpes zoster was the only infection with a statistically greater adjusted incidence rate in the 0.03% tacrolimus ointment group compared with vehicle; the events were five cases of *chicken pox*. Since no statistically significant difference was observed in the 0.1% tacrolimus ointment treatment group, it is likely that the five cases were by chance rather than drug/dose-related events.

Individual infection adverse events which had an adjusted 12-week incidence rate ≥5% in any treatment group or demonstrated a statistically significant treatment difference for adult patients (≥16 years of age) in the three pivotal studies are presented in Table 62.

Table 62: Summary of the Adjusted 12-Week Incidence Rate of Individual Infections†: Adult Patients (≥16 Years of Age) in the Three Pivotal Studies

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle	0.03%	0.1%	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	N=212	N=210	N=209				
	Rate ± Standard Error‡						
Flu Syndrome	19.3 ± 4.06	23.2 ± 3.28	30.8 ± 3.61	3.9 (-6.3, 14.2)	11.5 (0.9, 22.2)	0.451	0.034
Folliculitis	0.5 ± 0.51	6.2 ± 1.74	4.3 ± 1.50	5.7 (2.1, 9.3)	3.8 (0.7, 6.9)	0.002	0.016
Herpes Simplex	3.5 ± 1.81	5.0 ± 1.63	4.2 ± 1.57	1.4 (-3.3, 6.2)	0.6 (-4.1, 5.3)	0.553	0.790
Sinusitis	0.7 ± 0.68	3.9 ± 1.45	2.2 ± 1.09	3.2 (0.0, 6.3)	1.5 (-1.0, 4.0)	0.048	0.241
Skin Infection	10.6 ± 2.67	12.4 ± 2.50	4.7 ± 1.65	1.8 (-5.3, 9.0)	-5.8 (-12.0, 0.3)	0.617	0.063

Patient population: all randomized patients who received at least one dose of study drug.
CI: confidence interval.
Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In the ISS, this patient is categorized by true age.
† Based on infection cluster (predefined cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc.). Includes those infections that had an adjusted 12-week incidence rate of ≥5% in any treatment group or demonstrated a statistically significant treatment difference for adult patients (≥16 years of age) in the three pivotal studies combined.
§ From Normal Approximation test based on Kaplan-Meier Estimates. Statistical significance is indicated by p-values ≤0.05.
‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc.
Folliculitis = swollen or infected hair follicle.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: Section 8.4.13 (ISS Statistical Appendix 8.4.13.6.1.2.3).

In adult patients, the results mirrored those for the three studies combined except that there was a significantly greater adjusted incidence rate of sinusitis in the 0.03% tacrolimus ointment group compared with vehicle. (Of note, sinusitis was higher in the vehicle group in pediatric patients).

Reviewer's Comments:

Analysis of the data on the infections cluster of adverse events in these 3 controlled 12-week studies do not support a significant general increase in susceptibility of Tacrolimus treated atopic dermatitis patients (Table 55). Although some infections appear to be significantly increased in Tacrolimus treated patients over vehicle treated patients (flu syndrome, folliculitis, Varicella Zoster infection, Table 60), others appear to be significantly increased in vehicle treated patients over Tacrolimus treated patients (sinusitis in pediatric patients, Table 61).

It is not clear why the Varicella Zoster infections were significantly higher in 0.03% Tacrolimus treated patients over vehicle treated patients, but it was not higher in the 0.1% Tacrolimus treated patients. These cases were from different research centers in different States (Wake Forest University School of Medicine, Children Memorial Hospital, Advanced Healthcare of SC, Oklahoma university Health Science Center, and Virginia Clinical Research), ruling out a cluster of infection in one or few centers around a single or few cases as the cause for this result.

In conclusion, the possibility of increase in susceptibility to certain infections and in certain age groups cannot be excluded; neither can the possibility that the observed differences are random results due to the extensive multiplicity of the comparisons. However, the statistically significant increased infections have been already included in the adverse events in Table 59 which is recommended for inclusion in the label.

8.5.1.4 Serious Adverse Events

The incidence of serious adverse events in the three pivotal studies is summarized in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.6.1 and 8.4.13.6.6.2).

A total of 16 (1.6%) patients (7 patients in the pediatric study and 9 patients in the adult studies) experienced one or more serious adverse events during treatment. The incidence of serious adverse events during treatment was similar for vehicle-treated (1.5%) and tacrolimus ointment-treated (1.7%) patients. Serious adverse events are presented for the pediatric pivotal study in Section 8.5.1.4.1 and for the two pivotal adult studies in Section 8.5.1.4.2. In addition, seven patients (4 vehicle and 3 tacrolimus ointment-treated patients) experienced a serious adverse event post-treatment. There were no patient deaths in these studies