8.5.1.4.1 Pediatric Study 97-0-037

Seven (2.0%) patients in the pivotal pediatric study experienced one or more serious adverse events during the treatment period of the study. A summary of these adverse events and their relationship to study drug is presented in Table 63.

Table 63: Treatment Emergent Serious Adverse Events in Pivotal Pediatric Study 97-0-037

Patient No. (Treatment Group)	Age (yrs)	COSTART Term	Why Serious	Application Site (yes/no)	Causal Relation	Change In Study Drug	Out-come	Onset/End Days
15704 (Vehicle)	3	Anaphylactoid Reaction† (to food)	6	No	None	N	R	4/4
156703 (0.03%)	3	Asthma	4	No	None	N	R	81/82
221703 (0.1%)	3	Dehydration	4	No	None	I	R	51/51
		Asthma	4	No	None	I	R	51/61
		Hypoxia	4	No	None	I	R	51/51
		Asthma	4	No	None	N	R	51/53
		Pneumonia	4	No	None	I	R	51/53
		Dyspnea	4	No	None	N	R	51/51
236701 (0.1%)	5	Skin Infection	4	Yes	None	N	R	58/64
		Anuria	4	No	None	N	R	58/58
		Cellulitis	4	Yes	None	N	R	58/64
173701 (0.1%)	6	Arthralgia	4	No	None	N	R	82/86
220751 (0.1%)	9	Asthma	4	No	None	I	R	51/55
216754 (0.1%)	12	Skin Erythema	6	Yes	Possible	R‡	R	5/6

Patient population: all randomized patients who received at least one dose of study drug.
Why serious adverse event: 4=hospitalization; 6=medical importance (as per FDA definition).
Change in study drug: N=none; I=interrupted; R=reduced. Outcome: R=recovered without sequelae.
† Patient No. 15704 had a history of food allergies.
‡ Patient No. 216754 stopped treating the forehead area temporarily, but continued treating the remainder of affected body surface area.
Study 97-0-037 (Pediatric).
Source: Study Report R98-0214-506-C3-E (Appendices 14.4.4.1 and 14.5).

One pediatric patient had a treatment emergent serious adverse event that was considered possibly related to study drug. Patient No. 216754 (0.1% tacrolimus ointment), a 12-year old male of mixed race with severe atopic dermatitis experienced mild skin erythema on the forehead on study days 5 and 6. The patient stopped treating the forehead area, but continued treating the remainder of affected body surface area. The event, which was considered possibly related to

study drug, was considered to be of medical importance since the patient was seen in the emergency room and was given Benadryl®. The patient recovered with no sequelae, resumed treatment to the forehead, had no further episodes of erythema, and completed the study.

In addition to the treatment emergent serious adverse events listed in Table 63, three pediatric patients experienced serious adverse events after the end of treatment. The serious adverse events that occurred during the posttreatment period are presented in Table 64. None of these events were considered to be related to study drug by the investigator; all three patients recovered without sequelae.

Table 64: Posttreatment Serious Adverse Events in Pivotal Pediatric Study 97-0-037

Patient No. (Treatment Group)	Age (yrs)	COSTART Term	Why Serious	Application Site (yes/no)	Causal Relation	Out-come	Last Application Day	Onset/ End Days
216706 (Vehicle)	2	Asthma	6	No	None	R	1	2/7
84753 (Vehicle)	11	Lack of Drug Effect	4	Yes	None	R	22	28/40
156712 (0.1%)	5	Asthma (wheezing)	6	No	None	R	88	91/92

Patient population: all randomized patients who received at least one dose of study drug.
Why serious adverse event: 4=hospitalization; 6=medical importance (as per FDA definition).
Outcome: R=recovered without sequelae.
Study 97-0-037 (Pediatric).
Source: Study Report R98-0214-506-C3-E (Appendices 14.4.4.1 and 14.5).

Of the four cases of asthma in the tacrolimus ointment groups (3 treatment emergent, 1 posttreatment), three patients (Patient Nos. 156703, 156712, and 220751) had a history of asthma. The remaining patient (Patient No. 221703), 3 years of age, had asthmatic bronchitis coincident with pneumonia and had a history of hay fever.

8.5.1.4.2 Adult Studies 97-0-035 and 97-0-036

Nine (1.4%) patients in the pivotal adult studies experienced one or more serious adverse events during the treatment period of the study. A summary of these adverse events and their relationship to study drug is presented in Table 65.

Table 65: Treatment Emergent Serious Adverse Events in the Pivotal Adult Studies

Patient No. (Treatment Group)	Age (yrs)	COSTART Term	Why Serious	Application Site (yes/no)	Causal Relation	Change In Study Drug	Out-come	Onset/End Days
89518 (Vehicle)	72	Cerebrovascular Accident	2	No	None	I	RS	25/26
198536 (Vehicle)	26	Leukopenia	6	No	Possible	D	R	11/35
216613 (Vehicle)	51	Skin Infection	4	Yes	None	D	R	12/17
231606 (Vehicle)	41	Hernia†	4	No	None	N	R	21/21
19504 (0.03%)	38	Asthma	4	No	None	D	R	43/50
198534 (0.1%)	25	Leukopenia	6	No No No	Possible Possible Possible	I I D	P P P	8/15 15/22 22/ongoing
215510 (0.1%)	39	Skin Infection	6	Yes	None	N	R	78/98
44611 (0.1%)	37	Pneumonia Dehydration Anorexia Hemoptysis Stomatitis	4 4 4 4 4	No No No No No	None None None None None	I I I I I	R R R R R	17/31 17/31 17/31 17/31 17/31
85611 (0.1%)	37	Vomiting‡	6	No	None	N	RS	5/6

Patient population: all randomized patients who received at least one dose of study drug. Why serious adverse event: 2=life-threatening; 4=hospitalization; 6=medical importance (as per FDA definition). Change in study drug: N=none; I=interrupted; D=permanently discontinued. Outcome: R=recovered without sequelae; RS=recovered with sequelae; P=persistent condition at the last study visit. † Patient No. 231606 had a history of hiatal hernia. ‡ Patient No. 85611 was diagnosed as having a peptic ulcer. Studies 97-0-035 (Adult) and 97-0-036 (Adult). Source: Study Reports L1999000006 and L1999000008 (Appendices 14.4.4.1 and 14.5).

Two patients experienced serious adverse events of leukopenia during Study 97-0-035:

- Patient No. 198536 (vehicle), a 26-year-old white female, had *leukopenia* reported on Day 11 based on a reduction in neutrophil and white blood cell (WBC) counts. This event was

considered possibly related to study drug and the patient discontinued the study on Day 21. Neutrophil and WBC values for this patient were as follows (L=value below normal range):

Day	Neutrophils (%)	WBC ($x10^9$/L)
Baseline	64.6	4.8
11	51.5L	3.3L
25†	48.6L	3.7L
35†	58.1	4.3

† 4 and 14 days after discontinuation of the study drug.

- Patient No.198534 (0.1% tacrolimus), a 25-year-old black female, had *leukopenia* reported on Day 8 based on a reduction in neutrophil and WBC counts. This event was considered possibly related to study drug and study drug was interrupted from Day 9-19 and permanently discontinued on Day 23. The patient was subsequently diagnosed with benign neutropenia of blacks by an outside consultant. Neutrophil and WBC values for this patient were as follows (L=value below normal range):

Day	Neutrophils (%)	WBC ($x10^9$/L)
Baseline	58.8	3.4L
8	36.4L	2.2L
15	63.3L	3.0L
22	25.0L	2.0L
29†	42.9L	2.1L
44†	33.3L	2.1L

† 6 and 21 days after discontinuation of the study drug.

Note that the neutrophil and WBC counts fluctuated below the lower limit of the normal range both during treatment and posttreatment, consistent with a diagnosis of benign neutropenia of blacks.

In addition to the treatment emergent serious adverse events listed in Table , four patients (two patients in the vehicle treatment group and two patients in the 0.1% tacrolimus ointment treatment group) experienced a serious adverse event after study completion. The serious adverse events that occurred during the posttreatment period are presented in Table 66. None of these events was considered to be related to study drug by the investigator.

Table 66: Posttreatment Serious Adverse Events in the Pivotal Adult Studies

Patient No. (Treatment Group)	Age (yrs)	COSTART Term	Why Serious	Application Site (yes/no)	Causal Relation	Out-come	Last Application Day	Onset/End Days
19503 (Vehicle)	69	Skin Carcinoma	6	No	None	R	8	26/26
84505 (Vehicle)	75	Acute Kidney Failure	4	No	None	R	6	7/9
221619 (0.1%)	24	Flu Syndrome	4	No	None	U	1	32/unknown
231605 (0.1%)	39	Manic Depressive Reaction†	4	No	None	RS	68	98/111

Patient population: all randomized patients who received at least one dose of study drug.
Why serious adverse event: 4=hospitalization; 6=medical importance (as per FDA definition).
Outcome: R=recovered without sequelae; U=unknown; RS=recovered with sequelae.
† Patient had a history of manic behavior.
Studies 97-0-035 (Adult) and 97-0-036 (Adult).
Source: Study Reports L1999000006 and L1999000008 (Appendices 14.4.4.1 and 14.5).

8.5.1.5 Summary of Adverse Events Leading to Discontinuation

The incidence of adverse events leading to discontinuation in the three pivotal studies is summarized in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.6.7.1 and 8.4.13.6.7.2; for appendix titles see List of Appendices).

8.5.1.5.1 Overall

In the three pivotal studies, a total of 68 patients had adverse events that led to discontinuation from the study. The more common adverse events leading to discontinuation were pruritus, skin erythema, the sensation of skin burning, and skin infection. The incidence of these adverse events is summarized in Table 67.

Table 67: Incidence of Adverse Events Leading to Discontinuation†: Three Pivotal Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Number of Patients		N=328	N=328	N=327
Discontinuation Due to Adverse Event‡		35 (10.7%)	19 (5.8%)	14 (4.3%)
Skin & Appendages	Pruritus	19 (5.8%)	9 (2.7%)	6 (1.8%)
	Skin Erythema	12 (3.7%)	2 (0.6%)	1 (0.3%)
	Skin Burning	8 (2.4%)	7 (2.1%)	7 (2.1%)
	Skin Infection	5 (1.5%)	0	0

Patient population: all randomized patients who received at least one dose of study drug.
† Experienced by at least 1% of patients in any treatment group. A patient could have discontinued for more than one adverse event.
‡ 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.
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 8.4.13.6.7.1)

A higher percentage of vehicle-treated patients than tacrolimus ointment-treated patients discontinued due to an adverse event.

8.5.1.5.2 By Age

A total of 18 (5.1%) pediatric patients (2-15 years of age) had adverse events that led to discontinuation from the study (9 [7.8%] in the vehicle treatment group, 6 [5.1%] in the 0.03% tacrolimus ointment treatment group, and 3 [2.5%] in the 0.1% tacrolimus ointment treatment group). Twelve of the 215 patients 2-6 years of age (5.6%) and 6 of the 137 patients 7-15 years of age (4.4%) discontinued from the study due to an adverse event.

A total of 50 (7.9%) adult patients (≥16 years of age) had adverse events that led to discontinuation from the study (26 [12.3%] in the vehicle treatment group, 13 [6.2%] in the 0.03% tacrolimus ointment treatment group, and 11 [5.3%] in the 0.1% tacrolimus ointment treatment group).

The incidence of the more common adverse events leading to discontinuation in the three pivotal studies is summarized by age in Table 68.

Table 68: Summary of the Incidence of Common Adverse Events† Leading to Discontinuation By Age: Three Pivotal Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Pediatric Patients (2-15 years of age)‡		*N=116*	*N=118*	*N=118*
Any Adverse Event		9 (7.8%)	6 (5.1%)	3 (2.5%)
Skin & Appendages	Pruritus	2 (1.7%)	2 (1.7%)	0
	Skin Erythema	2 (1.7%)	1 (0.8%)	0
	Skin Burning	2 (1.7%)	1 (0.8%)	0
	Skin Infection	2 (1.7%)	0	0
2-6 years of age		*N=72*	*N=74*	*N=69*
Any Adverse Event		5 (6.9%)	6 (8.1%)	1 (1.4%)
Skin & Appendages	Pruritus	1 (1.4%)	2 (2.7%)	0
	Skin Erythema	2 (2.8%)	1 (1.4%)	0
	Skin Burning	2 (2.8%)	1 (1.4%)	0
	Skin Infection	0	0	0
7-15 years of age‡		*N=44*	*N=44*	*N=49*
Any Adverse Event		4 (9.1%)	0	2 (4.1%)
Skin & Appendages	Pruritus	1 (2.3%)	0	0
	Skin Erythema	0	0	0
	Skin Burning	0	0	0
	Skin Infection	2 (4.5%)	0	0
Adult Patients (≥16 years of age)		*N=212*	*N=210*	*N=209*
Any Adverse Event§		26 (12.3%)	13 (6.2%)	11 (5.3%)
Skin & Appendages	Pruritus	17 (8.0%)	7 (3.3%)	6 (2.9%)
	Skin Erythema	10 (4.7%)	1 (0.5%)	1 (0.5%)
	Skin Burning	6 (2.8%)	6 (2.9%)	7 (3.3%)
	Skin Infection	3 (1.4%)	0	0

Patient population: all randomized patients who received at least one dose of study drug.
† Experienced by at least 1% of patients in any treatment group regardless of age as shown in Table. A patient could have discontinued for more than one adverse event.
§ 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.
‡ 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 8.4.13.6.7.2).

Very few non-skin adverse events led to discontinuation in both pediatric and adult patients (fever, 2 patients; allergic reaction, 1 patient; face edema, 1 patient; photosensitivity reaction, 1 patient; exacerbation of untreated area, 1 patient; leukopenia, 2 patients; edema, 2 patients; arthralgia, 1 patient; hyperesthesia, 1 patient; asthma; 3 patients).

8.5.1.6 Clinical Laboratory Profile Summary

The mean change from baseline for selected clinical laboratory parameters in the three pivotal studies is presented in the NDA, ISS, Section 8.4.13 (ISS Statistical Appendices 8.4.13.7.1 and 8.4.13.7.2).

In the three pivotal studies, no consistent changes or notable differences among treatment groups in laboratory profile were observed. Mean and median values for BUN, GGTP, magnesium, creatinine, SGOT, SGPT, and WBC for the individual studies and the three studies combined remained within normal ranges at Weeks 1, 3, and 12. Overall, the incidence of laboratory abnormalities for these parameters during treatment time points Weeks 1, 3, and 12 was similar to that observed at baseline. These laboratory parameters are affected with the systemic use of tacrolimus. Absence of notable changes in these parameters with treatment supports the lack of systemic effect with topically applied tacrolimus.

Reviewer's Comments:

The conclusions made by the sponsor in the above sections 8.5.1.4, 8.5.1.5 and 8.5.1.6 appear to be reasonable and in agreement with the data in the individual studies. Although it was stated previously (section 8.5.1.2.4) that the treatment site adverse events were mild or moderate in severity, it is to be noted that some of these AE resulted in discontinuations (Table 68). It does not appear necessary to include any additional information from these sections in the label.

8.5.2 Two Pivotal Long-term Studies

8.5.2.1 Exposure

Exposure to tacrolimus ointment in the long-term studies is summarized in Table 69.

Patients in both studies applied ointment on most days of study participation (median 97%, pediatric study; 94%, adult study).

Blood was collected for the determination of tacrolimus concentration in the long-term adult study (Study FG-06-12). Most patients (77%, 241/312) had a highest individual concentration below 1 ng/mL. Only one patient had a concentration ≥5 ng/mL; the highest individual blood concentration for this patient was — ng/mL on Day 171. All other concentrations for this patient were below 1 ng/mL.

Table 69: Summary of Exposure to Tacrolimus in Long-Term Studies: Pediatric Study 96-0-025 and Adult Study FG-06-12

		Study 96-0-025 Pediatric Patients	Study FG-06-12 Adult Patients
Total Number of Patients		255†	316‡
Percent BSA Treated at Start of Therapy§			
2 – 6 years	N	115	
	Mean ± SD	42.3 ± 26.2	—
	Median (range)	35.7	
7 – 15 years	N	140	
	Mean ± SD	39.2 ± 23.4	—
	Median (range)	35.2	
≥18 years	N		302
	Mean ± SD	—	30.3 ± 17.4
	Median (range)		29.2
Total Number of Days of Treatment			
	N	255	313¶
	Mean ± SD	279.3 ± 114.3	180.6 ± 94.9
	Median (range)	338	170
Total Grams of Ointment Used#			
	N	111	Available only by time increment [Table 13.3.2]
	Mean ± SD	567.1 ± 806.0	
	Median (range)	308	
Daily Ointment Use (g) During Treatment#			
	N	111	Available only by time increment [Table 13.3.3]
	Mean ± SD	2.2 ± 3.2	
	Median (range)	1.3	
Days of Treatment as % of # of Days in Study			
	N	255	313¶
	Mean ± SD	87.1 ± 20.8	86.4 ± 16.8
	Median (range)	97	94.5

SD: standard deviation. BSA: body surface area. † All enrolled patients who received at least one dose of study drug. ‡ All enrolled patients who received at least one dose of study drug and had postbaseline data.
§ In Study 96-0-025, %BSA to be treated at baseline and in Study FG-06-12, %BSA treated during Week 1.
# Most patients returned most of their tubes, however calculations were based on the number of patients who returned all tubes of ointment throughout the entire 1-year study and had the tubes weighed. ¶ Three patients had no diary information. Other patients were assumed to have applied ointment on days with missing diary information. †† Patient No. 158102 was treated for 2 days, however, the difference in tube weight (dispensed-returned) was recorded as 0. Source: Study Report R98-0213-506-C3-E (Tables 13.3.1, 13.3.2, and 13.3.3, and Appendices 14.4.1.1, 14.4.2.1, 14.4.2.2, and 14.4.3.1) and Study Report FG98-506-07 (Table 13.3.1 13.3.2, 13.3.3, and 13.3.4).

Reviewer's Comments:

1- **Ointment usage in study FG-06-12**: The sponsor could not provide the mean or median values of "Total grams of ointment used" or "Daily ointment use (g) during treatment" for this study in the above table (table 69 = NDA, ISS, Table 30). Tables 13.3.2 and 13.3.3 of the NDA ISS are provided as an appendix to this review (Attachments 2 and 3, respectively). These tables provide these values over certain time periods of the study. The cumulative mean total ointment use in grams was 476.15 for 256 patients from day 1 to the end of month 5, 514.85 for 144

patients from day 1 to the end of month 6, 897.88 for 92 patients from day 1 to the end of month 11, and 856.47 for 35 patients from day 1 to the end of month 12 in this study (Table 13.3.2). These figures give a reasonable estimate for the degree of exposure in this study.

2- **Tacrolimus blood concentrations in Study FG-06-12:** The sponsor has provided a summary of these blood levels in Tables 7.4 and 7.5 of this study report. Copies of these tables are provided below.

Table 7.4 Tacrolimus Concentrations in Whole Blood — Number of Patients (%) (N =316)

ng/mL	n	< LOQ §	<1	1 to <2	2 to <5	≥5
Day 1	288	249 (86.5)	38 (13.2)	1 (0.3)	0	0
Week 1	282	37 (13.1)	214 (75.9)	22 (7.8)	9 (3.2)	0
Week 2	273	16 (5.9)	222 (81.3)	27 (9.9)	8 (2.9)	0
Month 1	274	26 (9.5)	221 (80.7)	26 (9.5)	1 (0.4)	0
Month 3	251	40 (15.9)	188 (74.9)	21 (8.4)	2 (0.8)	0
Month 6	219	55 (25.1)	147 (67.1)	12 (5.5)	4 (1.8)	1 (0.5)
Month 12	62	9 (14.5)	48 (77.4)	3 (4.8)	2 (3.2)	0
Overall maximum †	312	5 (1.6)	236 (75.6)	53 (17.0)	17 (5.4)	1 (0.3)

† Based on the maximum of each patient during the study
§ LOQ, the limit of reliable quantification, was — ng/mL
Source: Table 13.3.5

APPEARS THIS WAY ON ORIGINAL

Table 7.5 Tacrolimus Concentrations in Whole Blood (ng/mL) (N = 316)

Visit	n	Mean ± SD ‡	Median (min-max)
Day 1	288	0.04±0.14	0 —
Week 1	282	0.47±0.57	0.32 —
Week 2	273	0.48±0.52	0.30 —
Month 1	274	0.39±0.41	0.26 —
Month 3	251	0.31±0.41	0.18 —
Month 6	219	0.34±0.63	0.14 —
Month 12	62	0.28±0.46	0.13 —
Overall maximum †	312	0.71±0.72	0.51 —

† Based on the maximum of each patient during the study
‡ Values below the limit of reliable quantification — ng/mL) were set to 0
Source: Table 13.3.6

The sponsor's comments on these tables were the following: "These blood concentration data show that absorption of tacrolimus was very low. Most patients (241/312, 77.2%) had a maximum tacrolimus concentration below 1 ng/mL. The maximum concentration observed during the course of the study was — ng/mL, and this represents the only patient (Patient Number 4408) who experienced a concentration above 5 ng/mL. This blood concentration occurred on Day 171; all other measurements for this patient were below 1 ng/mL. He was withdrawn from the study on Day 302 because of lack of drug effect."

The present reviewer agrees with the sponsor's conclusion regarding these tables. However, as previously noted (reviewer comments, section 8.5.1.1) it appears that certain patients do not show any blood levels whereas others tend to show high blood levels in most of their blood samples. This does not appear from an examination of the above tables (7.4 & 7.5) because they show means and medians of all patients at different times. To confirm this possibility in the present study, the reviewer examined the Data Listings 14.4.4.3, Tacrolimus Blood Levels (ng/mL), in this study report. This is a 122-page table including data for 312 patients. Only the first 40 pages of this data listing were analysed, finding 19 patients with blood levels 1 ng/mL or above.

Eight patients had blood levels above 2 ng/mL (up to — ng/mL, patients #: 1206, 1306,1311, 1317, 1708, 2108, 2214, and 2216). Of all the blood concentrations determined (n=40) for these patients at points of time other than the first day which is usually below the level of quantification (average 5 determinations / patient, at times from first week to 6th month), only two values (2/40) were below level of detection — ng/mL) and six values (6/40) were below 0.5 ng/mL (4 of these were in a single patient, # 1317). The remaining 32 values included 27 values (27/40) that were above 1 ng/mL.

Eleven patients had blood levels between 1.0 and 2.0 ng/mL (patients # 1101, 1207, 1303, 1304, 1605, 1705, 1819, 2002, 2106, 2114 and 2212). Of all the blood concentrations determined (n=51) for these patients at points of time other than the first day which is usually 0 ng/mL (average 5 determinations / patient, at times from first week to 6th month), only three values (3/51) were below level of detection — ng/mL) and 16 values (16/51) were below 0.5 ng/mL. The remaining 32 values (32/51) were above 0.5 ng/mL.

Review of SAS data sets for this issue was requested from the Statistical Review Team in the Division (11/15/00). The analysis showed the following of all blood samples other than the baseline sample:

1- For all patients (n = 239) who had Tacrolimus blood levels **below 1 ng/mL** at all time points, the mean value of their blood levels, excluding the highest value in each patient, was **0.174**, and SD was 0.139 ng/mL.

2- For all patients (n = 70) who had Tacrolimus blood levels of **1 ng/mL or higher** at any time point, the mean value of their blood levels, excluding the highest value in each patient, was **0.720**, and SD was 0.396 ng/mL, a statistically significantly higher level than the previous set (#1).

3- For all patients (n = 291) who had Tacrolimus blood levels below **2 ng/mL** at all time points, the mean value of their blood levels, excluding the highest value in each patient, was **0.250**, and SD was 0.235 ng/mL.

4- For all patients (n = 18) who had Tacrolimus blood levels of **2 ng/mL or higher** at any time point, the mean value of their blood levels, excluding the highest value in each patient, was

1.070, and SD was 0.493 ng/mL, a statistically significantly higher level than the previous set (#3).

5- For all patients who had Tacrolimus blood levels **below 1 ng/mL** at all time points, **87.8%** had no more than one sample (out of 5 samples per patient in average) above 0.5 ng/mL.

6- For all patients who had Tacrolimus blood levels of **1 ng/mL or higher** at any time point, only **5.7%** had no more than one sample (out of 5 samples per patient in average) above 0.5 ng/mL.

7- For all patients who had Tacrolimus blood levels of **2 ng/mL or higher** at any time point, only **7.7%** had no more than one sample (out of 5 samples per patient in average) above 0.5 ng/mL.

These results confirmed that certain patients tend to have high blood concentrations of Tacrolimus. The reasons for this tendency are unknown, and there is no way of predicting these persons at present. This is further supported by the following analysis, provided by the sponsor in another place in this study report (Section 9.1.5.3): "To select adverse events that could have a relationship to systemic exposure, an exploratory analysis was done to compare the incidence of adverse events between patients who maintained tacrolimus blood concentrations < 1 ng/mL during the entire course of the study and those who experienced a concentration ≥ 1 ng/mL at any time during the study. Diarrhea and herpes simplex were detected using Fisher's exact test (Appendix 14.2.2.2 of the study report). Diarrhea was experienced by six patients (6/242, **2.5%**) in the <1 ng/mL group and by six patients (6/70, **8.6%**) in the ≥ 1 ng/mL group. However, only one of the tacrolimus measurements was taken within one week of the event. Herpes simplex was experienced by 25 patients (25/242, **10.3%**) in the <1 ng/mL group and by 15 patients (15/70, **21.4%**) in the ≥ 1 ng/mL group. Blood levels of ≥1 ng/mL occurred within seven days of the infection for only four patients."

APPEARS THIS WAY
ON ORIGINAL

8.5.2.2 Adverse Events

The incidence of adverse events in the long-term studies is summarized in Table 70.

APPEARS THIS WAY
ON ORIGINAL

Table 70: Summary of the Incidence of Adverse Events: Long-Term Studies

	Incidence	
	Study 96-0-025 Pediatric Patients	Study FG-06-12 Adult Patients
Number of Patients	255†	316‡
Overall Adverse Event	222 (87.1%)	292 (92.4%)
Overall Drug-Related Adverse Event	123 (48.2%)	232 (73.4%)
Application Site Adverse Event	138 (54.1%)	248 (78.5%)
Drug-Related Application Site Adverse Event	115 (45.1%)	223 (70.6%)
Nonapplication Site Adverse Event	196 (76.9%)	238 (75.3%)
Drug-Related Nonapplication Site Adverse Event	37 (14.5%)	62 (19.6%)
Infection§	169 (66.3%)	206 (65.2%)
Drug-Related Infection	33 (12.9%)	88 (27.8%)
Adverse Event Resulting in Discontinuation	10 (3.9%)	28 (8.9%)
Serious Adverse Event	21 (8.2%)	16 (5.1%)

† All enrolled patients who received at least one dose of study drug.
‡ All enrolled patients who received at least one dose of study drug and had postbaseline data.
Drug-related: possibly or probably related to study drug, assessment missing, or not assessable based on the investigator's assessment.
§ Based on an *infection cluster* of COSTART terms (e.g., flu syndrome, herpes simplex, chills and fever, etc.).
Source: Study Reports R98-0213-506-C3-E (Tables 13.5.1, 13.5.2.3, 13.5.3.1, 13.5.3.4, 13.5.6.1, 13.5.6.2, 13.5.6.4, 13.5.9.1, 13.5.9.4, 13.5.11.1, and 13.5.12.1) and FG-98-506-07 (Tables 13.5.1, 13.5.5.1, and 13.5.6.1).

In the long-term studies, the more common adverse events were skin burning, pruritus, and flu-like symptoms. As in the 0.1% tacrolimus ointment group in the 12-week pivotal studies (Table 49, section 8.5.1.2.2.1 of this review), the incidence of application site adverse events was higher in adults than in children. The incidence of application site adverse events was similar in the 12-week pivotal studies and the long-term studies (pediatric application site: 12-week study 54.2%, long-term study 54.1%; adult application site: 12-week study 78.9%, long-term study 78.5%). This is not surprising since these events tended to occur early.

For pediatric study 96-0-025, the incidence of adverse events is presented by individual age for patients aged 2-6 years (NDA Section 8.4.13, ISS Statistical Appendix 8.4.13.8.4). The overall incidence of adverse events for 2, 3, 4, 5, and 6 year olds was comparable to that for the entire study population; however the adverse event profiles for each age were determined from small groups of patients and therefore quite variable. The most common adverse event for each age was: 2-year olds, flu-like symptoms (11/20, 55%); 3-year olds, flu-like symptoms (10/32, 31%); 4-year olds, asthma (8/21, 38%); 5-year olds, flu-like symptoms and skin burning (each 6/20, 30%); and 6-year olds, asthma and skin burning (each 6/22, 27%).

The more common application site adverse events in both long-term studies were skin burning, pruritus, skin erythema, and skin infection. Skin burning is a coded term that represents a wide range of investigator terms, such as *burning, burning sensation, warmth sensation, hot feeling, soreness*, and *stinging*. Skin infection reflects the natural history of moderate to severe atopic

dermatitis and may also reflect the occlusive nature of the vehicle. The prevalence of these application site adverse events was highest during the first few days of treatment and decreased over time (NDA Study Reports: Study 96-0-025, Table 13.5.5.2; Study FG-06-12, Table 13.5.2.4).

The more common nonapplication site adverse events were flu-like symptoms, headache, and fever in pediatric Study 96-0-025 and flu-like symptoms and allergic reaction in adult Study FG-06-12. Except for flu-like symptoms, which showed an apparent seasonal effect (NDA Study Reports: Study 96-0-025, Appendix 14.3.4.5; Study FG-06-12, Appendix 14.3.4.6.7), there was no marked increase or decrease in the prevalence of any nonapplication site adverse event over time. The incidence of flu-like symptoms is within that expected for the general population (e.g., Center for Disease Control, 1994 prevalence of flu in the United States was 35%). The incidence of nonapplication site adverse events, including infections, did not increase with increased length of study drug exposure or amount of ointment used (NDA Study Reports: Study 96-0-025, Table 13.5.8; Study FG-06-12, Table 13.5.7.1).

Reviewer's Comments:

1- A complete list of all adverse events in these two long-term studies is needed for labeling. Adverse events occurring in 1% or more of the safety evaluable population should be included in the label. Tables providing this information were found in the appendices of the individual studies: Table 13.5.1 for study 96-0-25 (pediatric) and table 13.5.1.1 for study FG-06-12 (adult).

2- These tables are better combined with similar tables from the 3 controlled pivotal studies (see reviewer's comments on section 8.5.1.2.1) for inclusion in the label. Therefore, a table combining all AE with incidence of 1% or more in either the combined adult 12 week studies (97-0-035, -036), the pediatric 12 week study (97-0-037), the long-term adult study (FG-06-12) or the long-term pediatric study (96-0-25) was requested from the sponsor in a teleconference on the 26th of October 2000. This table was provided in submission to the NDA dated 11/10/00 (Attachment 4).

8.5.2.3 Hazard Rate Analysis of Adverse Events

APPEARS THIS WAY
ON ORIGINAL

Reviewer's Comments:

The long-term safety studies are important in showing whether there are any adverse events that may occur more frequently as the treatment is continued for longer periods of time. This information can be obtained from a comparison of daily hazard rates over periods of time. For this reason, the statistical reviewers requested such an analysis from the sponsor in March 15, 2000, with additional clarifications in a teleconference in April 10, 2000. The sponsor's

response to this specific request was submitted in April 21, 2000, in Attachment 3. This consisted of data pooled from the patients treated with 0.1% Tacrolimus ointment in the 12 week studies (97-0-035, -036 and –037) and the long-term studies (96-0-025 and FG-06-12), comparing the average daily hazard rates over three periods: day 1-90, day 91-182 and day 183-366. This information was reviewed by the statistical reviewer, who summarized the AE with an increasing estimated hazard rate over the time periods in a table (Statistical review, Table 11).

The highest rates noticed in this table (Table 11 of FDA statistical review) were in the **lymphadenopathy group of AE** (0.075, 0.093, and 0.111 for the 3 time periods, respectively). This was followed by seborrhea: 0.000, 0.023 and 0.066. All other AE in that table had rates ranging between 0.000 and 0.046. The high and progressively increasing hazard rates of lymphadeopathy in this analysis raised some concerns, especially when considered together with the preclinical toxicology studies showing high incidence of lymphomas in mice treated topically with 0.1% Tacrolimus ointment. Further detailed study of these cases of lymphadeopathy was, therefore, undertaken.

On preliminary examination of the data on lymphadenopathy, the total number of cases reported in the global experience in the NDA was **23 subjects** (= 0.7%, NDA, ISS, Appendix 8.4.13.10.3.1). An **additional 10 cases** were reported in the 120-day safety update (Table 7, study 97-0-038: 8 lymphadenopathy, one lymphoma and one lymphoma like reaction). Examination of case report forms for a sample of these patients revealed that the majority were lymphadenitis, although few were unexplained enlargements of lymph nodes. Therefore, a request was made to the sponsor in a teleconference on 10/26/00 to provide an updated full description of all lymphadenopathy cases in patients treated with Tacrolimus ointment.

The requested information was submitted on 11/7/00. According to the sponsor, these 33 cases represent 0.8% (33/4205), and 73% of them (24/33) were lymphadenitis secondary to concurrent inflammatory processes such as tonsillitis or skin infection. As summarized in Table 1 of this submission, the sponsor has concluded that all cases were either explained by a current process, or have resolved except:

1- Case 042119 of study 96-0-025: Axillary lump coded as lymphadenopathy. Therapy was not discontinued and event resolved (313 days).
2- Case 231801 of study 97-0-038: Parotid lymphoma, with evidence that it was a pre-existing condition.
3- Case 251816 of study 97-0-038: Mycosis fungoides (Cutaneous T-cell lymphoma).

On review of the case narratives, the following was noted:

1. Case 042119 of study 96-0-025: Axillary lump coded as lymphadenopathy. Therapy was not discontinued and event resolved (313 days). Resolution of this case is doubtful because the report showed that it existed from day 72 till day 384 when the patient was discontinued from the study and the lump was reported to have recovered (suddenly!) without any treatment.
2. Case 231801 of study 97-0-038: Parotid lymphoma, with evidence that it was a pre-existing condition. The evidence that it was a pre-existing condition is very weak because it is based on the patient recalling that he had it for about one year, whereas it was not reported in any of the earlier examinations of this patient.

3. Case 251816 of study 97-0-038: Mycosis fungoides (Cutaneous T-cell lymphoma). This case raises concerns of misdiagnosis and mistreatment. However, there was no evidence of any worsening of the condition due to the mistreatment or the delay of proper treatment. The course of this condition is usually very slowly progressive. Warning does not seem to be necessary.
4. Eight other cases were found to be reported as related to the treatment by the evaluating physician, ongoing, lost for follow up, remain unexplained and/or their recovery is doubtful:
   - Case 043143 of study 96-0-025: Posterior cervical lymph nodes palpable on day 357. Condition was ongoing at end of study (considered related), and in continuation study 97-0-038 (case 043801). He was discontinued from the latter study after 5 months due to noncompliance and no additional F/U was available.
   - Case 237512 of study 97-0-035: Positive axillary nodes started on day 72 and ongoing at discharge. No F/U available. Relation to photosensitivity eruption is possible.
   - Case 00001703 of study FG-06-12: Swollen lymph nodes in the neck noticed on day 95 and considered related. Reason unknown, reported to have "recovered" on discharge from study (day 112) without treatment. This recovery appears doubtful.
   - Case 00002705 of study FG-06-12: Severe AE, related, enlarged lymph nodes on day 29 in axillary and inguinal areas. No infection reported, but skin soreness on day 9 and swelling on day 16. No additional F/U available. Treatment was interrupted and patient discontinued because of AE on day 16.
   - Case 00003802 of study FG-06-12: Mild AE, related, left axillary adenopathy on day 332, patient continued on study FG-06-21 but "unavailable for additional F/U at present."
   - Case 00003814 of study FG-06-12: Mild AE, related, left axillary adenopathy on day 170, did not resolve and no F/U available. Blood levels of Tacrolimus ranged from [redacted] ng/mL from week 1 to month 6. No infectious etiology reported. Folliculitis was already resolved on day 145.
   - Case 00006407 of study FG-06-18: Inguinal adenopathy, mild, noticed on day 22, unresolved and no F/U available. Presumed to be due to persistent foot dermatitis (incidence not reported).
   - Case 221816 of study 97-0-038: Enlarged lymph nodes in the neck noticed on day 351, etiology unknown. On day 382, it was reported as recovered without any treatment. Its sudden disappearance after 31 days is doubtful.

8.5.2.4 Serious Adverse Events

There were no patient deaths during either long-term study. Serious adverse events are summarized in Tables 71 and 72 below.

In pediatric Study 96-0-025, 21 patients (8.2%) experienced one or more serious adverse events. The most common serious adverse event was asthma, occurring in 10 patients; each of these patients had a prior history of asthma. Three adverse events (anaphylactoid reaction, anaphylactoid reaction to food, asthma) were considered life-threatening; however none of these events were considered to be related to study drug and none led to any change in study drug. All

of these events might be anticipated in a population with underlying atopic diathesis. Three serious adverse events were considered potentially related to study drug (skin infection, asthma, and Kaposi's varicelliform eruption [eczema herpeticum]).

In adult Study FG-06-12, a total of 16 patients (5.1%) experienced one or more serious adverse events; five of these events were assessed as having a causal relationship to the study drug. Except for an accidental injury that was considered life-threatening, all serious adverse events involved hospitalization.

Table 71: Serious Adverse Events in Long-Term Studies: Pediatric Study 96-0-025

Patient No.	Age (yrs)	COSTART Term	Why SAE	Application Site (Yes/No)	Relationship (Yes/No)	Study Drug†	Out-come	AE Days
11112	2	Pneumonia	3	No	No	NC	R	26/33
		Asthma	8	No	No	NC	R	26/28
		Flu syndrome	8	No	No	NC	R	202/211
		Pharyngitis	8	No	No	NC	R	204/211
		Asthma	8	No	No	NC	R	275/275
11147	2	Skin infection	3	Yes	Yes	NC	R	34/45
		Asthma	3	No	No	NC	R	257/266
14177	2	Asthma	3	No	No	NC	R	173/175
42011	2	Viral meningitis	3	No	No	I	R	80/115
89150	3	Osteomyelitis	8	No	No	NC	P	366/-
195155	3	Asthma	3	No	No	NC	R	103/104
155122	4	Aortic stenosis#	3	No	No	R	R	186/186
156113	5	Asthma	3	No	No	NC	R	25/32
		Asthma	3	No	No	D‡	R	283/286
		Allergic reaction	3	No	No	NC	R	283/286
19009	6	Asthma	3	No	No	NC	R	322/323
160227	6	Anaphylactoid reaction to food	1	No	No	NC	R	243/243
19076	7	Anaphylactoid reaction##	1	No	No	NC	R	24/24
173070	7	Herpes simplex+	3	Yes	Yes	I	R	14/29
195168	7	Asthma	1	No	No	NC	R	244/244
221034	7	Hypoxia	3	No	No	NC	R	127/130
		Asthma	3	No	No	NC	S	127/130
		Pneumonia	3	No	No	NC	R	127/130
11046	9	Pharyngitis	3	No	No	NC	R	179/323
		Lymphadenopathy	3	No	No	NC	R	179/323
158040	9	Asthma	3	No	Yes	I	R	173/175
19111	10	Asthma	3	No	No	I	R	223/234
		Flu syndrome	3	No	No	I	R	223/229
219233	10	GI hemorrhage++	3	No	No	NC	R	308/309
107136	11	Skin infection	3	Yes	No	NC	P	100/-
42012	13	Corneal ulcer	3	No	No	I	S	11/42
14171	15	Accidental injury	3	No	No	NC	R	104/191

† Change in study drug administration; NC = No change; I = Interrupted; R = Reduced; D = Discontinued. SAE: serious adverse event. GI: gastrointestinal. Why SAE: 1=life threatening; 3=hospitalization; 8=medical importance (as per FDA definition). Outcome: R=recovered with no residual effects; S=recovered with sequelae; P=persistent condition at the last study visit. Adverse event days: /- Adverse event ongoing at end of study. # Patient was hospitalized for a procedure (balloon valvuloplasty) related to a pre-existing condition. ## Unknown etiology.
+ Kaposi's varicella (eczema herpeticum). ++ Endoscopy showed no active bleeding; small mucosal tear appeared to be healing. Patient on inhaled steroids for asthma. ‡ Patient prescribed prohibited medication (prednisone).
Source: Study Report R98-0213-506-C3-E (Appendices 14.4.4.1 and 14.6).

Table 72: Serious Adverse Events in Long-Term Studies: Adult Study FG-06-12

Pt. No.	Age (yrs)	COSTART Term (Investigator Term)	Why SAE	Relationship (Yes/No)§	Study Drug‡	Out-come	AE Days
1108	18	Lack of drug effect (flare-up of atopic dermatitis)†#	3	No	D††	P	74/88
2108	34	Herpes simplex (eczema herpeticum)†	3	Yes	I	R	55/64
2401	32	Herpes zoster (varicella)†#	3	Yes	I	R	140/148
		Routine procedure (corneal graft)	3	No	NC	R	104/104
3301	36	Skin infection (Staphylococcus superinfection)†	3	Yes	D††	R	132/147
		Routine procedure (ligation of fallopian tube)	3	No	NC	R	22/24
4408	20	Lack of drug effect (exacerbation of atopic dermatitis)†#	3	Yes	D††	P	270/-
1103	26	Fever (related to dehydration after travel)	3	No	NC	R	179/183
		Vertigo (related to dehydration after travel)	3	No	NC	R	179/183
1401	18	Keratitis (corneal ulcer)	3	No	NC	R	226/254
1707	28	Routine procedure (knee operation)	3	No	NC	R	146/150
1808	48	Benign breast neoplasm (benign tumour, left breast)	3	No	NC	R	51/64
2315	21	Gastroenteritis (food poisoning)	3	No	I	R	45/45
2316	20	Back pain (disc prolapse)	3	No	NC	R	55/89
2406	42	Routine procedure (routine operation to correct asymmetry of right iris)	3	No	NC	R	88/89
2603	43	Routine procedure (removal of ovarian cysts, ovaries and uterus)	3	No	I	R	36/36
4102	21	Accidental injury (car accident)	1	No	NC	S	136/247
4103	38	Unintended pregnancy	3	No	NC	R	22/67
		Abortion	3	No	NC	R	67/67
4107	24	Cellulitis	3	No	I	R	133/142
		Cellulitis	3	No	I	R	161/169
		Cellulitis	3	Yes	D††	P	198/-

SAE: serious adverse event. § Relationship yes: defined as highly probable, probable, possible, not assessable, or if relationship to study drug was missing. † Application site adverse events. # Both treated and non-treated areas affected. ‡ Change in study drug administration; NC = No change; I = Interrupted; D = Discontinued.

Why SAE: 1=life threatening; 3=hospitalization (as per FDA definition). Outcome: R=recovered with no residual effects; S=recovered with sequelae; P=persistent condition at the last study visit. Adverse event days: /- Adverse event ongoing at last visit or time of withdrawal. †† Patient prescribed prohibited medications.
Source: Study Report FG98-506-07 (Appendix 14.4.6.1).

A 6% incidence of Kaposi's varicelliform eruption has been reported in children with atopic dermatitis [Hauser, Prins & Lacour, 1996; Bonifazi et al.; 1985]. Affected patients are no longer primarily young children; the incidence in adults is increasing. For example a dermatological center in Europe reported on average 1 case per year between 1969 and 1989 and 10 – 15 cases per year between 1982 and 1986; approximately half of these cases were in adults [Bork & Bräuninger, 1988]. Therefore, the incidence of Kaposi's varicelliform eruption in the long-term core studies (one child, <1%; six adults, 2%) was not higher than one would anticipate in this population.

Reviewer's Comments:

The above-cited articles were reviewed and do not provide sufficient basis for drawing the conclusion that the observed incidence of Kaposi's varicelliform eruption is consistent with background incidence rates in patients with atopic dermatitis. It is possible that use of PROTOPIC Ointment may be assoicated with an increased risk of developing Kaposi's varicelliform eruption.

8.5.2.5 Adverse Events Leading to Discontinuation:

In pediatric Study 96-0-025, ten patients (3.9%) had an adverse event that led to discontinuation; three of these patients had adverse events considered to be related to study drug (SGOT and LDH increased, skin infection and skin burning, and maculopapular rash). In the case of increased SGOT and LDH, this 3-year-old black male entered the study with elevated SGOT (48 U/L) and LDH (381 U/L) and these parameters increased slightly during treatment (Day 15, SGOT 51 U/L, LDH 393 U/L).

In adult Study FG-06-12, 28 patients (8.9%) had an adverse event that resulted in discontinuation. Investigators attributed the withdrawal to an adverse event for 13 of these patients; an additional 15 patients had a reason other than adverse event given as the primary reason for withdrawal but had *permanently discontinued* indicated on the adverse event case report form. The more common application-site adverse events associated with discontinuation were lack of drug effect, skin infection, pruritus, and skin burning. In two patients, herpes simplex infection led to study discontinuation; the investigator term for one of these infections was eczema herpeticum.

Summaries of the adverse events leading to discontinuation in pediatric Study 96-0-025 and adult Study FG-06-12 are presented in Tables 73 and 74.

Table 73: Adverse Events Leading to Discontinuation in Long-Term Studies: Pediatric Study 96-0-025

Patient No.	Age (yrs)	COSTART Term	Application Site (Yes/No)	Relationship (Yes/No)	Adverse Event Days	Out-come	Last Dose Day
14177	2	Asthma	No	No	281/285	R	281
158047	3	LDH increased†	No	Yes	15/-	P	24
		SGOT increased†	No	Yes	15/-	P	
89110	5	Anaphylactoid reaction#	No	No	29-29	R	29
156113	5	Asthma	No	No	283-286	R	282
221016	6	Bronchitis	No	No	121/-	P	126
153045	8	Fungal dermatitis	Yes	No	8-35	R	13
220086	8	Skin infection	Yes	No	197-214	R	197
		Infection	No	No	197-214	R	
225249	9	Skin infection	Yes	Yes	221/-	P	264
		Skin burning##	Yes	Yes	260/-	P	
215006	14	Folliculitis	Yes	No	44-59	R	46
195165	15	Maculopapular rash	Yes	Yes	143-323	R	184

Patient population: all enrolled patients who received at least one dose of study drug.
SGOT = serum glutamic oxaloacetic transaminase. LDH = lactate dehydrogenase.
Outcome: R=recovered with no residual effects; P=persistent condition at the last study visit.
Adverse event days: /- adverse event ongoing at end of study.
† Patient No. 158047 had elevated LDH and SGOT at baseline.
# Patient allergic to grass, cats, and dogs; reaction occurred 3-4 hours after morning application; treated with Benadryl®.
Pain due to infected atopic dermatitis.
Source: Study Report R98-0213-506-C3-E (Appendices 14.4.4.1 and 14.6).

Table 74: Adverse Events Leading to Discontinuation in Long-Term Studies: Adult Study FG-06-12

Pt. No.	Age (yrs)	Event (COSTART Term)	Causal Relation†	Day of Withdrawal	Reason for Withdrawal
Application Site Adverse Events					
1108	18	Lack of drug effect§	No	94	Noncompliance
1204	23	Herpes simplex	Yes	94	Adverse event
1315	58	Lack of drug effect§	No	7	Required topical steroids
1604	39	Lack of drug effect§	No	28	Lack of efficacy
2104	35	Lack of drug effect§	Yes	152	Required topical steroids
2108	34	Herpes simplex (eczema herpeticum)	Yes	141	Adverse event
2109	63	Pruritus	Yes	179	Adverse event
2609	34	Urticaria§	Yes	160	Adverse event
2704	37	Pruritus and skin burning	Yes	15	Adverse event
2705	35	Skin infection‡	Yes	29	Adverse event
2906	18	Lack of drug effect§	Yes	8	Lack of efficacy
3102	46	Lack of drug effect§	Yes	237	Lack of efficacy
3301	36	Skin infection	Yes	150	Required topical steroids
3306	42	Skin infection§	Yes	88	Required topical steroids
3507	42	Skin burning	Yes	7	Adverse event
3903	38	Skin infection	Yes	209	Adverse event
3908	26	Allergic reaction§ and lack of drug effect§	No	92	Lack of efficacy
4002	18	Pruritus§, pustular rash§, skin burning§, and skin disorder§	Yes	16	Adverse event
4104	28	Lack of drug effect§	No	169	Required topical steroids
4302	38	Pruritus§	Yes	57	Adverse event
4408	20	Lack of drug effect§ and skin infection	Yes	302	Lack of efficacy
4415	31	Lack of drug effect§ and pustular rash§	No	8	Lack of efficacy

Table continued on next page

(Table continued)

Pt. No.	Age (yrs)	Event (COSTART Term)	Causal Relation†	Day of Withdrawal	Reason for Withdrawal
Nonapplication Site Adverse Even.					
2005	27	Liver function tests abnormal††	Yes	134	Adverse event
2205	25	Unintended pregnancy	No	15	Pregnancy
2304	20	Eczema	No	251	Required topical steroids
2705	35	Lymphadenopathy‡	Yes	29	Adverse event
3906	18	Unintended pregnancy	No	343	Pregnancy
4107	24	Cellulitis	Yes	201	Adverse event
4201	21	Unintended pregnancy	No	112	Pregnancy

† Defined as highly probable, probable, possible, not assessable, or if relationship to study drug was missing.
§ At both treated and non-treated areas.
‡ This patient had lymphadenopathy (enlarged lymph nodes) at a non-treated site associated with a skin infection at a treated area.
†† This 27-year-old male had elevated SGOT and SGPT at Week 1 and Months 2 and 3. The elevated levels resolved at Month 4 at the time of study drug discontinuation. The patient was withdrawn based on Day 110 values (SGOT 53 U/L, SGPT 120 U/L); Month 4 values were SGOT 24 U/L and SGPT 33 U/L.
Source: Study Report FG98-506-07 (Appendix 14.4.6.2).

8 5.2.6 *Laboratory investigations:*

No trends in laboratory profile suggestive of a safety concern with long-term use were observed in either long-term study (NDA, Study 96-0-025, Table 13.6; Study FG-06-12, Table 13.6.1).

The assessments in adult Study FG-06-12 for immunocompetence (CD_4 and CD_8 counts and the Recall Antigen Test) did not change over time providing supporting evidence that tacrolimus ointment has no effect on systemic immunocompetence. Mean and median CD_4 and CD_8 counts were similar at all visits during the study and within normal range. CD_4 and CD_8 counts allow a rough estimate of T-cell function; thus, these findings suggest that there was no change in humoral T-cell activity during treatment for up to one year. Mean Mérieux scores were 8.3 ± 7.6 on Day 1, 7.0 ± 3.7 at Month 6, and 9.4 ± 5.5 at Month 12. The mean number of positive antigens was 1.3 ± 1.2 on Day 1, 1.5 ± 1.3 at Month 6, and 1.8 ± 1.4 at Month 12. Based on the frequency of the number of positive reactions at Day 1, Month 6 and Month 12 and a shift analysis of the number of positive reactions on Day 1 versus that at Month 6, there was no change over time. Based on these results, tacrolimus ointment had no systemic effect on cell-mediated immunity in this long-term study (NDA, Study FG-06-12, Tables 13.8.1, 13.8.2, 13.8.3, 13.8.4, and 13.8.5).

8.5.2.7 *Exposure and Adverse Events:*

In order to explore potential relationship between drug exposure over time and the incidence of adverse events, time to onset analyses were performed for adverse events considered to be of particular interest in this patient population. These events do not include local irritation events since these have been demonstrated to occur early (generally during the first week) in treatment and might be anticipated given the very sensitive nature of the skin in patients with atopic dermatitis. Analyses were performed using data from the five core studies; the three vehicle-controlled, 12-week pivotal Phase 3 studies (Studies 97-0-037, 97-0-035, 97-0-036) and the two long-term safety studies (Study 96-0-025 and FG-06-12) which involved a total of 1556 treated patients. Note that all five studies contributed to the analyses from Day 1 through Day 89 but that only long-term study patients (treated with 0.1% tacrolimus ointment) were included from Day 90 onward.

As shown in Section 8.4.13 of the NDA (ISS Statistical Appendix 8.4.13.9), hazard rates for adverse events (e.g., flu syndrome, herpes simplex, herpes zoster, headache, folliculitis, etc.) either remained the same or decreased over time for all treatment groups. Therefore, there is no indication of increased risk for these events over time, even with long-term use of tacrolimus ointment.

In addition, in the long-term studies, the incidence of nonapplication site adverse events, including infections, did not increase with increasing duration of exposure (NDA, Study 96-0-025, Table 13.5.7; Study FG-06-12, Table 13.5.7.1).

Reviewer's Comments:

The above conclusions (sections 8.5.2.4 – 8.5.2.7) of the sponsor appear to be reasonably supported by the submitted data in general. However, a different hazard rate analysis has been discussed previously (Reviewer's comments, section 8.5.2.3) with the results indicating an increased rate of lymphadenopathy.

Also, it is important to comment on the results of the laboratory investigations (Blood chemistries, hematology and immunological evaluations, section 8.5.2.6 of this review) that these are mostly averages, medians and percentiles of the whole population. They cannot show if there is any correlation with Tacrolimus blood levels. This can be only obtained by comparison of individual patients results in comparison with their Tacrolimus blood levels.

8.5.3 Global Safety

8.5.3.1 Adverse Events in the Global Experience:

The global experience with tacrolimus ointment is based on similarly structured/coded demographic, exposure and adverse event data from 28 Phase 1, 2 and 3 studies conducted in the United States, Europe or Japan (see Table 1 in this Review).

Worldwide, a total of 3446 patients/subjects have applied tacrolimus ointment and were evaluable for safety in these 28 studies; 1528 (44%) of these were male and 1918 (56%) were female. The age of patients/subjects ranged from 2 to 85 years (mean ± standard deviation, 27.7 ± 15.1 years) with 287 patients 2-6 years of age, 378 patients 7-15 years of age, 2726 patients/subjects 16-64 years of age, and 55 patients/subjects ≥65 years of age. A total of 1677 (49%) patients/subjects were white, 439 (13%) were black, and 1291 (38%) were oriental (NDA Section 8.4.13, ISS Statistical Appendices 8.4.13.10.1.5, 8.4.13.10.1.6, and 8.4.13.10.2.1).

[Note: These studies include 302 patients treated only with the 0.3% or 0.5% concentrations of tacrolimus ointment which are not targeted for commercial development.]

The adverse event profile in the 28 studies combined is consistent with that observed in the three pivotal Phase 3 studies and the two long-term Phase 3 studies. The incidence of treatment emergent adverse events for the 28 Phase 1, 2, and 3 studies combined is presented in the NDA Section 8.4.13 (ISS Statistical Appendix 8.4.13.10.3.1). The more common adverse events included the sensation of skin burning, pruritus, skin erythema, flu-like symptoms, and skin tingling.

Reviewer's Comments:

1- On comparison of all AE in the global experience (NDA, Section 8.4.13, ISS Appendix 8.4.13.10.3.1) with the Overall AE in the three pivotal 12-week studies (NDA, Section 8.4.13, ISS Appendix 8.4.13.6.1.1), it was found that all AE in the former with incidence rates 1% or higher were included in AE occurring at 1% or more in either 0.03% or 0.1% ointment groups in the latter studies, except:

	Adverse Event	Incidence in: Global	in 12 week studies	
1-	Fungal Dermatitis (Skin and Appendages)	1.2%	0.9%,	0.6%
2-	Lack of Drug Effects (Body as a Whole)	1.1%	0.6%,	0.0%
3-	SGPT Increased (Metabolic and Nutr.)	1.6%	0.0%,	0.3%
4-	SGOT Increased (Metabolic and Nutr.)	1.0%	0.0%,	0.6%
5-	Leukocytosis (Hemic and Lymphatic)	1.2%	----	----

It is important to be sure these AE will be included in the label.

2- Tacrolimus Blood Levels: Due to the importance of Tacrolimus blood co. ..ntrations as previously discussed (see reviewer's comments in sections 8.5.1.1.3 and 8.5.2.1), a comparison of the distribution of these levels in the 5 pivotal studies and the global experience was carried out. This issue is discussed in the Biopharm Review, and the results are summarized in a table (see Biopharm Review) showing distribution of maximum blood concentrations across the different studies. The data in this table show higher concentrations in the global experience as compared to the 5 pivotal studies as shown in the following examples:

   1- In study FJ-111, a long-term (2 years) adult open-label study using 0.1% Tacrolimus ointment, the highest reported blood concentration was — ng/mL, whereas in the closely similar pivotal study FG-06-12 the highest blood concentration was — ng/mL, and the highest reported blood concentration in all pivotal studies (97-0-036, adult) was — ng-mL.

   2- Also, in study FJ-111, concentrations above 5 ng/mL were noticed in 21/562 patients (3.7%), whereas in the closest pivotal study (FG-06-12) the corresponding figure was 1/311 patients (0.3%).

   3- In study 95-0-009, a phase 2 pediatric (ages 3-6 years) dose-escalation study using 0.03% and 0.1% formulations for up to 3 weeks, the highest reported blood concentration was — ng/mL (0.1% formulation), whereas in the closely similar pivotal study 97-0-037 the highest blood concentration was — ng/mL (0.1% formulation. It is to be noted also that in this study (95-0-009), the Tacrolimus blood concentrations were generally much higher with the 0.1% formulation (highest — ng/mL, 0.5- <5 ng/mL in 67% of patients) in comparison to the 0.03% formulation (highest — ng/mL, 0.5- <5 ng/mL in 45% of patients).

8.5.3.2 *Adverse Events in Phase 1 Studies:*

A total of 585 healthy adult subjects and 14 patients applied tacrolimus ointment at concentrations ranging from 0.03% to 0.3% and were evaluable for safety in eight Phase 1 studies. These included 481 (80%) female subjects and 118 (20%) male subjects ranging from 18 to 85 years of age (mean ± standard deviation, 41.6 ± 13.2 years). The majority (79%) of these subjects were white and 20% of the subjects were black (NDA Section 8.4.13, ISS Statistical Appendix 8.4.13.10.2.2). The overall incidence of treatment emergent adverse events among these subjects was 11.5% (69/599). The overall incidence of adverse events in the Phase 1 studies combined is presented in Section 8.4.13 of the NDA (ISS Statistical Appendix 8.4.13.10.3.2). The more common adverse events included pruritus (2.3%), headache (2.3%), the sensation of skin burning (2.2%), pharyngitis (2.0%), and rhinitis (1.8%).

8.5.3.3 *Adverse Events in Phase 2 and 3 Studies:*

In the 20 Phase 2 and 3 studies 2847 patients applied tacrolimus ointment at concentrations ranging from 0.03% to 0.5% and were evaluable for safety. These included 1410 (50%) male patients and 1437 (50%) female patients ranging from 2 to 81 years of age (mean ± standard deviation, 24.8 ± 13.7 years). A total of 1202 (42%) patients were white, 317 (11%) were black, and 1291 (45%) were oriental (Section 8.4.13 of the NDA, ISS Statistical Appendix 8.4.13.10.2.3). The adverse event profile for these 20 Phase 2 and 3 studies combined is presented in Section 8.4.13 of the NDA (ISS Statistical Appendix 8.4.13.10.3.3). The more common adverse events included the sensation of skin burning (30.6%), pruritus (21.1%), skin erythema (20.9%), flu-like symptoms (12.1%), and skin tingling (9.9%).

For comparative purposes, those adverse events which were common (≥5% of patients in any treatment group) in the combined Phase 3 pivotal studies are shown with raw incidence in all Phase 2 and 3 studies combined in Table 75.

Table 75: Overall Incidence of Selected Adverse Events: Global Experience Phase 2 and Phase 3 Studies

	Treatment Group				Total
	Concentration of Tacrolimus Ointment				
	0.03%	0.1%	0.3%	0.5%	
Number of Patients	N=579	N=1966	N=254	N=48	N=2847
Body As a Whole					
Flu Syndrome	73 (12.6%)	267 (13.6%)	5 (2.0%)	0	345 (12.1%)
Fever	28 (4.8%)	74 (3.8%)	3 (1.2%)	0	105 (3.7%)
Allergic Reaction	26 (4.5%)	120 (6.1%)	0	0	146 (5.1%)
Nervous System					
Headache	48 (8.3%)	144 (7.3%)	4 (1.6%)	0	196 (6.9%)
Respiratory System					
Cough Increased	25 (4.3%)	65 (3.3%)	1 (0.4%)	0	91 (3.2%)
Asthma	16 (2.8%)	88 (4.5%)	3 (1.2%)	0	107 (3.8%)
Skin & Appendages					
Pruritus	173 (29.9%)	394 (20.0%)	34 (13.4%)	1 (2.1%)	602 (21.1%)
Skin Burning	195 (33.7%)	599 (30.5%)	68 (26.8%)	9 (18.8%)	871 (30.6%)
Skin Erythema	88 (15.2%)	469 (23.9%)	30 (11.8%)	9 (18.8%)	596 (20.9%)
Skin Infection	32 (5.5%)	90 (4.6%)	0	0	122 (4.3%)

Patient population: safety evaluable patients in 20 Phase 2 and 3 studies worldwide.
Selected: adverse events which were common (≥5% in any treatment group) in the three Phase 3 pivotal studies 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.
Source: Section 8.4 13 (ISS Statistical Appendix 8.4.13.10.3.3).

The integrated safety profile for all Phase 2 and 3 studies (Section 8.4.13 of the NDA, Statistical Appendices 8.4.13.10.3.3, 8.4.13.10.4.1, 8.4.13.10.4.2, 8.4.13.10.4.3, 8.4.13.10.4.4, and 8.4.13.10.4.5) is consistent with that observed in each of the three pivotal Phase 3 studies (Studies 97-0-037, 97-0-035, and 97-0-036), as well as the combined analyses for these three studies (Section 8.4.3.3 of the NDA), and the two long-term Phase 3 studies (Section 8.4.3.4 of the NDA).

In the three pivotal Phase 3 studies, no notable differences in adverse event profile between races were observed. However, in the Phase 2 and 3 studies combined, in which 45.3% of patients were oriental (versus 5.3% in the three pivotal studies), although there were no race-related adverse events, several notable differences were apparent for oriental patients. Several adverse events, including the sensation of skin burning, pruritus, skin infection, flu-like symptoms, and headache occurred less frequently among oriental patients than black or white patients. The incidence of skin tingling was greater for oriental patients than for black or white patients. Oriental patients treated with 0.1% tacrolimus ointment also had a notably greater incidence of skin erythema and folliculitis than black or white patients (Section 8.4.13 of the NDA, ISS Statistical Appendix 8.4.13.10.4.4). This may be a true racial difference or may be due to global differences in adverse event reporting/translation by both the physician and patient which remain despite efforts to structure/code adverse event data in a consistent manner.

8.5.3.4 Adverse Events from Other Sources:

A literature search for the period 1975 through April 30, 1999 was conducted. Adverse events identified in published literature are of the type and incidence observed in the clinical studies presented herein. Databases and key words utilized in this search are listed, and relevant articles are tabulated and summarized, in Section 8.7.2.

Reports to the Sponsor of serious adverse events (received prior to June 15, 1999) in ongoing US, European, and Japanese clinical studies are summarized in Table. Note that US and European serious adverse events are irrespective of causality while Japanese events are only those considered by the investigator and/or sponsor to be related to study drug.

Table 76: Serious Adverse Events in Ongoing United States‡, European and Japanese Clinical Studies

Body System	COSTART Term	Number of Patients
Ongoing US Study 97-0-038† - irrespective of causality		
Body as a Whole	Allergic Reaction	1
	Anaphylactic Reaction	1
	Cellulitis	2‡‡
	Chills	1
	Hernia	1
	Infection	2
	Accidental Injury	2
	Overdose	1
	Chest Pain$	1
Cardiovascular	Hypertension$	1
	Hypotension	1
	Syncope	1
Digestive	Colitis	1
	Diarrhea	1
	Pancreatitis	1
Endocrine	Diabetes Mellitus++	1
Hemic & Lymphatic	Lymphadenopathy	1
	Lymphoma Like Reaction$$	1
Metabolic & Nutritional	Peripheral Edema	1
Musculoskeletal	Arthritis	1
	Joint Disorder	1
	Bone Disorder	1
Respiratory	Asthma	10
	Bronchitis	1
	Pharyngitis	1
	Pneumonia	3
	Sinusitis	1
Skin & Appendages	Carcinoma Skin	4§§
	Erythema Nodosum	1
	Rash	2

	Pustular Rash	2
	Vesiculobullous Rash	1
	Sweating	1
	Urticaria	2
Special Senses	Cataract	1
	Glaucoma¥	1
Urogenital	Breast Abscess	1
	Uterine Hemorrhage	1
	Uterine Fibroids Enlarged	1
Ongoing European Study FG-06-18§ - irrespective of causality		
Cardiovascular	Arrhythmia Atrial	1
	Bradycardia	1
Respiratory	Hyperventilation	1
Skin & Appendages	Eczema	1
	Pruritus	1
Special Senses	Conjunctivitis	1
	Ophthalmitis	1
Ongoing European Study FG-06-19# - irrespective of causality		
Body as a Whole	Allergic Reaction	1
	Accidental Injury	2
	No Drug Effect	2
Respiratory	Asthma	1
Skin & Appendages	Angioedema	1
	Eczema	1
	Rash	1
Ongoing European Study FG-06-21☆ - irrespective of causality		
Body as a Whole	Anaphylactic Reaction	1
	Infection	1
	Accidental Injury	2
	No Drug Effect	1
Cardiovascular	Myocardial Infarction	1##
Respiratory	Asthma	5
Skin & Appendages	Skin Carcinoma	1
	Urticaria	1

Ongoing Japanese Study FJ-111; Post 1 Year Data†† - those considered to be related to study drug by the investigator and/or sponsor		
Body as a Whole	Infection	1
	Abscess	1
Skin & Appendages	Vesiculobullous Rash	6@

SAE: serious adverse event.
† Patients in US Study 97-0-038 received 0.1% tacrolimus ointment.
‡ No SAEs have been reported among patients in ongoing US Study 99-0-054.
§ Patients in European Study FG-06-18 received either 0.03% tacrolimus ointment, 0.1% tacrolimus ointment, or 0.1% hydrocortisone butyrate ointment; study is still blinded.
# Patients in European Study FG-06-19 received either 0.03% tacrolimus ointment, 0.1% tacrolimus ointment, or 1% hydrocortisone acetate ointment; study is still blinded.
+ Patients in European Study FG-06-21 received 0.1% tacrolimus ointment.
†† Patients in Japanese Study FJ-111 received 0.1% tacrolimus ointment. Note: Pancytopenia was reported for a 33-year-old female patient in Study FJ-111. However, following an extensive workup, the relationship to the study drug was assessed as *unlikely*. The pancytopenia was attributed to an herbal medicine the patient was taking at the time (Byakkokaninjinto [Kampo]). A report was sent to the FDA prior to determination of the relationship.
$ Patient had a history of hypertension and was undergoing job stress for the previous 6 to 8 months.
++ During a routine workup at his annual physical examination, the patient was noted to have type II diabetes mellitus. The patient had a known history of asthma, reflux esophagitis, mild hyperlipidemia, hiatal hernia, and iron deficiency anemia.
$$ This 68 year old male patient presented with a mass that had been present for 1 year. This adverse event was not considered to be related to study drug (*definitely not*).
¥ Patient had glaucoma in both eyes; patient had a prior history of severe vernal keratoconjunctivitis with bilateral corneal shield ulcers and left eye pseudophobia.
‡‡ One patient experienced two episodes.
§§ One patient experienced three episodes. Three of these cases were deemed by the investigator to have no relationship to study drug. The remaining patient with a basal cell carcinoma and squamous cell carcinoma had at least two of three lesions present before starting treatment; the investigator deemed the event to have an unlikely relationship to study drug. All four cases involved individuals 61-72 years of age. One of these four patients was considered by the investigator to be at high risk for skin cancer as he had a very fair complexion and had experienced severe sun damage/high sun exposure early in his adult life. Another of the four patients had a prior history of basal cell carcinoma and should not have been enrolled in the clinical study.
Patient No. 1501, a 59-year-old male, died as a result of myocardial infarction; the event was considered definitely not related to study drug. The patient, who had been treated with 0.1% tacrolimus ointment for 139 days, had a history of non-insulin dependent diabetes mellitus.
@ This represents six cases of Kaposi's varicelliform eruption.

8.6 Conclusions:

1- **Topical safety studies**: Review of the results of the "Repeated Insult Patch Test" has indicated that the product was a mild contact sensitizer in 0.5% of the subjects tested, and that the vehicle ingredient(s) is the most likely sensitizing agent (see reviewer comments on section 8.2.2 in this review). This was further confirmed by the incidence of contact dermatitis in the 12 week controlled studies at a rate of 2.4% in the 0.03% Tacrolimus Ointment treated patients, 1.5% in the 0.1% Tacrolimus Ointment treated patients, and

0.9 % in the vehicle treated patients (see reviewer comments on section 8.5.1.2.1 in this review).

2- **Efficacy in adults**: The results of the two adult 12 week studies support the efficacy of both 0.03% and 0.1% Tacrolimus ointments in the treatment of signs and symptoms of atopic dermatitis in adults. It appears that there is advantage for having both concentrations available for treatment of adult patients because of the significantly higher efficacy of the 0.1% over the 0.03% ointment in the following sub-populations of patients: females, blacks, severe disease and extensive disease involvement (>75% BSA). The general superiority of the 0.1% over the 0.03% ointment in adults was confirmed in the primary efficacy parameter as well as most of the secondary efficacy parameters (see reviewer comments on section 8.3.1.4.2.2 in this review). Because higher blood levels of Tacrolimus may be more likely to occur with the 0.1% than the 0.03%, it seems safer to use the lower concentration for those patients who respond to it and also for maintenance of the response obtained with the higher concentration.

3- **Indication and usage in both adult and pediatric patients**: Because of the exclusion of patients with clinically infected atopic dermatitis from the three 12 week protocols, it is important to restrict the use to uninfected patients.

4- **Efficacy in pediatric patients**: The results of the pediatric 12 week study support the efficacy of both 0.03% and 0.1% Tacrolimus ointments in the treatment of signs and symptoms of atopic dermatitis in pediatric patients. However, no clinically or statistically significant differences could be detected in the efficacy of these two concentrations in the pediatric population or subpopulations either in the primary or secondary efficacy parameters (see reviewer's comments on sections 8.4.1.4.2 and 8.4.1.4.3 in this review). Because pediatric patients may absorb more of the Tacrolimus into their blood, and because of the expected long term exposure to the Tacrolimus ointment during their life, it seems that there is no sufficient justification for the use of the 0.1% ointment in pediatric patients.

5- Recurrences: Information about recurrences in the pivotal studies should be included in the label: 1) In the adult 12 week studies combined (97-0-035 and –036), the number of patients who had documented recurrences after being successfully treated (90% improvement or more) were 18/51 i.e. **35%** in the 0.03% tacrolimus arm (7/27 and 11/24) and 30/74 i.e. **41%** in the 0.1% tacrolimus arm (13/33 and 17/41). These recurrences occurred as early as 1 day, and as late as 26 days (mean = **7.6 days**) after discontinuation of treatment (see section 8.3.1.4.2.2-D of this review). 2) In the pediatric 12 week study (97-0-037), 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 (see section 8.3.1.4.3-D of this review). 3) In long-term studies of adults (FG-06-12) and children ((96-0-025), the patients used the Tacrolimus ointment >85% of

the days on study to control their atopic dermatitis (see sections 8.3.2.3.1 and 8.4.2.3.1 of this review).

6- **Tacrolimus blood levels**: The results of Tacrolimus blood concentration measurements in the 12 week controlled studies in adults and children (see reviewers comments on section 8.5.1.1) and in the adult pivotal long term study FG-06-12 (see reviewers comments on section 8.5.2.1) indicate that certain patients tend to get higher blood levels in most of their blood samples than other patients with similar severity, body surface area involved, Tacrolimus concentration used, age, and sex. Blood levels in the global studies (see reviewers comments on section 8.5.3.1) have reached as high as — ng/mL (study FJ-111, a long-term (2 years) adult open-label study), and as high as 4% of patients in one study (study FJ-111, 21/562) had concentrations above 5 ng/mL which is the trough level for maintenance of immunosuppression in transplant patients. Because of the possibility of late systemic adverse events (kidney failure, lymphoproliferative disorder) which may be correlated with systemic Tacrolimus levels, predicting these patients is very important, considering the benefit risk ratio in atopic dermatitis patients. However, analysis of the available data (see reviewers comments on sections 8.5.1.1 and 8.5.2.1) showed the lack of such predictors. This needs cautious safety labeling and should be addressed in phase 4 studies commitment.

7- **Adverse events in the label**: 1) All adjusted 12 week 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 (Tables 56, 57 and 58 of this review) have been combined in one table (Table 59 of this review) by the present reviewer. Because these adverse events are the most likely to be associated with the active ingredient in Tacrolimus ointment, this information appears to be of special importance and should be conveyed to the prescribing physician in the Physician Package Insert. 2) To include all adverse events occurring at a rate of 1% or more in either the adult 12 week studies, the pediatric 12 week study, the long term adult study, the pediatric long term study or in the global experience, the table provided by the sponsor in the 11/10/00 submission, attachment 4 (see reviewers comments on section 8.5.2.2 of this review) should be used, with the following events from global safety results (see reviewers comments on section 8.5.3.2 of this review) added:

Adverse Event	Incidence in: Global	in 12 week studies	
Fungal Dermatitis (Skin and Appendages)	1.2%	0.9%,	0.6%
Lack of Drug Effects (Body as a Whole)	1.1%	0.6%,	0.0%
SGPT Increased (Metabolic and Nutr.)	1.6%	0.0%,	0.3%
SGOT Increased (Metabolic and Nutr.)	1.0%	0.0%,	0.6%
Leukocytosis (Hemic and Lymphatic)	1.2%	----	----

8- **Additional safety points for label**: 1) As discussed in section 8.5.1.3.4 of this review, the possibility of an increase in susceptibility to certain infections in the general population or in certain age groups cannot be excluded. 2) Although it was stated that the treatment site adverse events were mild or moderate in severity, it is to be noted that some of these AE resulted in discontinuations (Table 68 of this review).

9- **Lymphadenopathy**: A comprehensive review of all the cases of lymphadenopathy in the global experience was carried out in collaboration with the sponsor (see reviewers comments on section 8.5.2.3 of this review). Of the 33 cases reported one case was cutaneous T-cell lymphoma that was misdiagnosed and treated as atopic dermatitis, a case of parotid lymphoma that may have appeared early during treatment, and 8 cases of lymph node enlargements that have not been clearly diagnosed and/or clearly resolved at the end of treatment. The majority of these 33 cases were lymphadenitis secondary to skin infection or tonsillitis. This needs cautious safety labeling and should be addressed in phase 4 studies commitment.

9 Labeling Recommendations

See "Conclusions" section

10 Recommendations

10.1 Approval, Approvable

It is recommended that the 0.03% Tacrolimus ointment be approved for both pediatric and adult patients with atopic dermatitis, and the 0.1% Tacrolimus ointment be approved for only the adult patients with atopic dermatitis provided that labeling changes as suggested in the "Conclusions" section and Phase 4 studies (as outlined below) are undertaken. It is recommended

10.2 Phase 4 Studies

To permit more complete assessment of the safety profile of Tacrolimus ointment in the treatment of atopic dermatitis, the following Phase 4 studies are suggested:

[

]

[ ]

11 Labeling changes

See labeling review

12 Financial Disclosure

As per FDA Form 3454, submitted September 8, 1999, Sponsor has certified that, in the five pivotal clinical studies performed in support of this NDA, no financial arrangements with investigators have been made where outcome affects compensation, and that the investigators had no proprietary interest in the product, or significant equity interest in the sponsor, or were the recipient of any significant payments of other sorts (as defined in 21 CFR 54.2). The certified studies were:

1- Study 96-0-025, pediatric long-term safety study,
2- Study 97-0-035, adult 12 week efficacy and safety study,
3- Study 97-0-036, adult 12 week efficacy and safety study,
4- Study 97-0-037, pediatric 12 week efficacy and safety study, and
Study FG-06-12, adult long-term safety study.

13 Signature block and distribution list

Medical Reviewer

Ranzy S. Labib, M.D., Ph.D.

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Okun
HFD-540/Medical Reviewer/Labib
HFD-540/Medical Officer/Mathis
HFD-725/Biostatistics Team Leader/Alosh
HFD-725/Biostatistician/Lu
HFD-880/Biopharm/Tandon
HFD-540/Pharm/Hill
HFD-540/Chemistry/Hathaway
HFD-540/Project Manager/Wright

/s/

Ramzy Labib
12/7/00 03:13:48 PM
MEDICAL OFFICER

Martin Okun
12/7/00 03:16:38 PM
MEDICAL OFFICER

Jonathan Wilkin
12/18/00 12:23:59 PM
MEDICAL OFFICER

Medical Officer's Review of NDA 50-777
Addendum # 1

DATE: 12/7/00

This is a copy of a Divisional letter which is referred to in my review as Attachment # 1.

Attachment # 1

NDA 50-777

Fujisawa Healthcare, Inc
Attention: Donald E. Baker, J.D.
Senior Director, Regulatory Affairs
Parkway North Center
Three Parkway North
Deerfield, Illinois 60015-2548

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Baker:

Please refer to your new drug application dated September 8, 1999, received September 9, 1999, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Protopic (tacrolimus) Ointment, 0.03 and 0.1%.

We also refer to your submissions dated October 21, November 9, and December 9, 1999; January 10, and 31, February 11, and March 13, 2000.

We are reviewing your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

CLINICAL

1. Please provide data on the relationship of blood levels of FK506 and subsequent development of lymphomas (or posttransplant lymphoproliferative disorders) in patients treated systemically with FK506 (Prograf). Please provide any available information concerning the relative risk of EBV seroprevalence for development of lymphomas (or posttransplant lymphoproliferative disorders) in patients treated systemically with FK506.

2. Please provide data on the chronology of lymphoma (or posttransplant lymphoprolieferative disorders) development in patients treated systemically with FD506. Please characterize the chronology of lymphomas (or posttransplant lymphoprolieferative disorders) development separately in pediatric and adult populations.

3. The Sponsor should clarify whether the lymphomas noted in the recipients of Prograf were of a B-cell or T-cell origin.

BIOPHARMACEUTICS

1. The Sponsor should conduct a population analysis of the plasma concentrations measured in Phase 2 and 3 Clinical Trials for 0.03, 0.1 and 0.3% tacrolimus ointment to obtain rough estimates of AUC. From Study 94-0-008, it appears that the plasma concentration profile is relatively flat at steady state. Hence, estimating AUCs from the random samples taken during clinical trials would provide a rough estimation of the AUCs at the to-be-marketed strengths of tacrolimus ointment.

2. The Sponsor should conduct a pharmacokinetic study in adult and pediatric patients with severe atopic dermatitis using the 0.1% tacrolimus ointment. The study should have enough patients, in both the adult and pediatric population, with acute atopic dermatitis, to evaluate any differences in pharmacokinetic parameters and should be conducted under the maximal use conditions associated with a maximum surface area coverage. Plasma sampling should be sufficient to evaluate relevant pharmacokinetic parameters.

PHARMACOLOGY/TOXICOLOGY

1. Please provide historical background incidence rates from the contract laboratory that conducted the 2 year mouse dermal carcinogenicity study for tacrolimus ointment for the following tumor types:
   a. Liver-Carcinoma
   b. Cervix-Stromal Cell Sarcoma
   c. Uterus-Leiomyoma

2. The Sponsor should clarify whether the lymphomas noted in the 2 year mouse dermal carcinogenicity study conducted for tacrolimus ointment were of a B-cell or T-cell origin, if known.

3. It is recommended that the Sponsor conduct a nonclinical study in minipigs, or other suitable species, to determine the concentration of tacrolimus in the regional lymph nodes that drain from the skin after topical tacrolimus ointment application to abraded or irritated skin. The purpose of this study is to determine if the concentration of tacrolimus in regional lymph nodes that drain from the skin is higher than or the same as the level of tacrolimus in the blood after topical administration. This information is necessary for the determination of human risk for lymphoma after topical

administration of tacrolimus ointment. It is recommended that the Sponsor submit the study protocol for this study to the Division for review prior to initiation of the study.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

Jonathan Wilkin, M.D.
Director
Division of Dermatologic
and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 50-777
HFD-540/Div. Files
HFD-540/M.Wright
HFD-540/Wilkin
HFD-540/Okun
HFD-540/Labib
HFD-540/Jacobs
HFD-540/Hill
HFD-725/Al-Osh
HFD-725/Lu
HFD-880/Tandon
HFD-880/Bashaw

Drafted by:MAW /March 29, 2000
Initialed by MKF/3/29/00:
final:3/29/00/MAW
filename: N50777IR

INFORMATION REQUEST (IR)

Medical Officer

Ramzy S. Labib, M.D., Ph. D.

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 50-777
Addendum # 2

DATE: 12/7/00

This is a copy of the sponsor's tables which are referred to in my review as Attachment #2 and 3.

TABLE 13.3.2

TACROLIMUS OINTMENT ADMINISTRATION - TOTAL OINTMENT USE (g)

	0.1% Tacrolimus N=316									
	N-	Mean	SD	Minimum	Maximum	10%	25%	50%	75%	90%
Total Ointment used during-:										
Week 1	314	39.46	34.04			4.44	12.19	30.22	59.26	92.94
Week 2	311	33.41	27.59			5.05	11.67	27.26	48.47	70.74
Month 1	302	127.46	98.30			21.98	50.55	102.73	183.45	257.69
Month 2	291	105.06	93.55			18.71	38.25	75.70	136.95	227.39
Month 3	284	89.69	86.56			13.15	27.00	57.73	122.77	208.20
Month 4	268	84.93	87.42			11.32	23.94	55.02	109.61	205.90
Month 5	257	79.31	84.30			10.66	25.17	50.85	101.14	188.41
Month 6	144	72.46	75.89			8.73	20.02	45.80	99.10	193.12
Month 7	98	78.59	99.84			6.86	21.05	49.56	102.89	183.62
Month 8	97	76.14	86.04			5.02	19.22	42.93	93.82	186.89
Month 9	94	72.19	77.30			5.93	17.48	47.36	107.44	158.22
Month 10	92	70.01	78.27			6.77	19.61	49.17	82.17	147.86
Month 11	92	80.84	90.95			9.35	22.38	54.08	104.03	204.50
Month 12	35	70.16	65.26			4.49	12.43	58.54	110.56	159.67

- In case of incomplete information about weight of ointment used, several assumptions were made, only patients who completed the time period were used for the calculations

TABLE 13.3.2 (continued)

TACROLIMUS OINTMENT ADMINISTRATION - TOTAL OINTMENT USE (g)

	0.1% Tacrolimus N=316									
	N-	Mean	SD	Minimum	Maximum	10%	25%	50%	75%	90%
Cumulative Total Ointment used from Day 1 to the End of-:										
Week 1	314	39.46	34.04			4.44	12.19	30.22	59.26	92.94
Week 2	311	72.68	58.59			11.43	24.47	59.29	105.84	157.47
Month 1	302	127.46	98.30			21.98	50.55	102.73	183.65	257.69
Month 2	291	231.68	181.87			46.87	96.57	178.64	335.41	483.84
Month 3	284	321.35	255.38			64.87	134.35	249.62	452.39	694.59
Month 4	268	398.54	329.75			80.49	152.74	304.81	557.50	894.37
Month 5	257	476.15	403.29			91.51	175.56	361.80	636.33	1004.9
Month 6	144	514.85	447.56			87.20	183.43	373.56	693.60	1117.2
Month 7	98	607.86	551.43			110.33	202.00	469.23	865.05	1296.6
Month 8	97	687.86	628.07			128.13	220.99	550.54	950.70	1395.0
Month 9	94	756.12	685.19			144.92	249.01	613.40	1066.7	1476.7
Month 10	92	817.04	755.69			153.43	292.91	628.22	1170.2	1558.1
Month 11	92	897.88	832.80			169.26	319.43	680.21	1247.5	1723.6
Month 12	35	856.47	600.40			159.64	315.87	728.23	1409.6	1638.3

- In case of incomplete information about weight of ointment used, several assumptions were made, only patients who completed the time period were used for the calculations

TABLE 13.1.3

TACROLIMUS OINTMENT ADMINISTRATION - OINTMENT USE PER APPLICATION DAY (g/day)

	0.1% Tacrolimus N=316									
	N-	Mean	SD	Minimum	Maximum	10%	25%	50%	75%	90%
Daily Ointment used during:										
Week 1	314	5.08	4.35			0.58	1.60	3.89	7.44	11.67
Week 2	310	4.95	4.12			0.89	1.76	4.15	7.02	10.65
Month 1	302	4.60	3.44			0.91	1.90	3.89	6.48	8.91
Month 2	291	3.56	3.05			0.79	1.39	2.65	4.65	7.61
Month 3	282	3.40	3.07			0.52	1.14	2.48	4.71	7.71
Month 4	265	3.15	3.05			0.47	1.01	2.21	4.30	7.08
Month 5	255	3.12	2.99			0.54	1.11	2.15	4.12	7.15
Month 6	143	2.91	2.83			0.39	0.93	2.05	3.61	7.09
Month 7	98	3.12	3.60			0.33	0.92	1.99	3.68	7.70
Month 8	97	2.91	2.98			0.28	0.77	1.98	3.98	6.24
Month 9	93	2.70	2.58			0.45	0.90	2.30	3.52	5.14
Month 10	91	2.76	2.86			0.45	1.00	1.91	3.65	5.14
Month 11	90	3.04	3.04			0.48	0.99	2.21	3.65	7.11
Month 12	34	3.13	3.15			0.38	0.87	2.34	3.97	8.75

- In case of incomplete information about weight of ointment used, several assumptions were made, only patients who completed the time period were used for the calculations
For days with no diary information patients were assumed to have applied the ointment

Medical Officer

Ramzy S. Labib, M.D., Ph. D.