Appendix I

Clinical Pharmacokinetics and Pharmacology Studies

Pharmacokinetic Studies				
Protocol Number	**Study Design**	**Patient Population [actual age]**	**Regimen**	**No. Treated†† (treatment group)**
FG-06-04‡ Phase 1 [R96-0025-506-C1B-E]	Double-blind, 4 way crossover pharmaco-kinetic study	Healthy subjects [aged 22-41 years]	0.03%, 0.1%, or 0.3% tacrolimus ointment or vehicle once daily for 14 days, 1000 cm^2 area	14
94-0-008† Phase 2 [R95-0085-506-C2-E and R95-0166-506-C1P-E]	Open-label pharmaco-kinetic study	Adult and pediatric atopic dermatitis patients [aged 5-75 years]	0.3% tacrolimus ointment once daily days 1, 8 twice daily on days 2-7; 50 to 5,000 cm^2 treated area	39
FJ-106§ Phase 2 [P98-0126-506-C2-E]	Open-label, pharmaco-kinetic / safety study	Adult patients with acute-type AD [aged 17-42 years]	Single application of 0.1% or 0.3% tacrolimus ointment	13 9 (0.1%) 4 (0.3%)
			0.1% tacrolimus ointment twice daily for 7 days	8 (0.1%)

†United States ‡Europe §Japan.
†† Number of patients who received at least one dose of study drug.

Clinical Pharmacology Studies				
Protocol Number [Company Report]	**Study Design**	**Patient Population [actual age]**	**Regimen**	**No. Treated‡‡ (treatment group)**
94-0-004† Phase 1-Patch Test [R95-0035-506-C1-E]	Open-label, intrasubject, repeated insult patch test study	Healthy subjects [aged 23-64 years]	0.03%, 0.1%, 0.3% tacrolimus ointment, vehicle, 0.005% calcipotriene, 1.0% hydrocortisone, 0.1% betamethasone valerate; patching repeated 9 times over 3 weeks	30

94-0-005† Phase 1-Patch Test [R95-0036-506-C1-E]	Open-label, intrasubject, photo-toxicity study	Healthy subjects [aged 23-44 years]	0.03%, 0.1%, 0.3% tacrolimus ointment, vehicle, 0.005% calcipotriene, 1.0% hydrocortisone, 0.1% betamethasone valerate; single application with or without UV irradiation	12
94-0-006† Phase 1-Patch Test [R95-0037-506-C1-E]	Open-label, intrasubject, photocontact allergy test study	Healthy subjects [aged 19-60 years]	0.03%, 0.1%, 0.3% tacrolimus ointment, vehicle, 0.005% calcipotriene, 1.0% hydrocortisone, 0.1% betamethasone valerate; 6 applications over 3 weeks with or without UV irradiation	30
94-0-007† Phase 1-Patch Test [R95-0010-506-C1-E]	Open-label, intrasubject cumulative irritation study	Healthy subjects [aged 18-63 years]	0.03%, 0.1%, 0.3% tacrolimus ointment, vehicle, 0.005% calcipotriene, 1.0% hydrocortisone, 0.1% betamethasone valerate, 0.5% sodium lauryl sulfate; patching repeated 18 times over 3 weeks	30
95-0-011† Phase 1-Patch Test [R96-0037-506-C1-E]	Double-blind, intrasubject, repeated insult patch test study	Healthy subjects [aged 18-85 years]	0.03%, 0.1%, or 0.3% tacrolimus ointment or vehicle; patching repeated 9 times over 3 weeks	229
97-0-026† Phase 1-Patch Test [R98-0118-506-C1-E]	Double-blind, intrasubject photocontact allergy test study	Healthy subjects [aged 18-65 years]	0.03% or 0.1% tacrolimus ointment or vehicle with or without UV irradiation; patching repeated 6 times over 3 weeks	228
FG-06-17‡ Phase 2*-PD [R97-0163-506-C2-E]	Double-blind, randomized, single-center clinical pharmacology (collagen synthesis) study	Healthy subjects and atopic dermatitis patients [aged 18-59 years]	0.1%, 0.3% tacrolimus ointment, betamethasone valerate ointment, and vehicle; two applications of each during 1 week, occlusion (abdomen, 4x4 cm); and twice daily for 2 weeks, lichenified elbow flexure (12 cm^2)	26 (12 subjects) (14 patients) [elbow flexure, 14 patients: 6 (0.1%); 8 (vehicle)]
97-0-030† Phase 2-PD [L1999 003123]	Double-blind, randomized, active control immuno-histological study (biopsy study)	Adult atopic dermatitis patients experiencing an acute flare [aged 18-81 years]	0.1% tacrolimus ointment or 0.1% triamcinolone acetonide ointment (TA) twice daily for 3 weeks	23 (12 tacrolimus) (11 TA)

† United States ‡ Europe
*Included as a Phase 1 study in global experience analysis in view of its *patch-test like* study design.
‡‡Number of patients who received at least one dose of study drug.
TA: Triamcinolone acetonide; PD: Pharmacodynamic
Three additional pharmacology studies, pharmacokinetic Studies FG-06-04, 94-0-008 and FJ-106 are described in below.

Appendix II

1 CLINICAL STUDIES

Pivotal Phase 3 Studies				
Study	**Description**	**Patients [actual age]**	**Regimen**	**No. Treated† (treatment group)**
97-0-037 [R98-0214-506-C3-E]	Double-blind, randomized study in patients with moderate or severe atopic dermatitis involving at least 10% of the body surface area	Children [aged 2-15 years] n=351	0.03% or 0.1% tacrolimus ointment or vehicle twice daily for up to 12 weeks	117(0.03%) 118 (0.1%) 116(vehicle)
97-0-035‡ [L1999 000006]		Adults [aged 15-77 years] n=304		103 (0.03%) 99 (0.1%) 102 (vehicle)
97-0-036 [L1999 000008]		Adults [aged 16-79 years] N=328		108 (0.03%) 110 (0.1%) 110 (vehicle)
† Number of patients who received at least one dose of study drug. ‡ Patient No. 84515 was enrolled in this adult study despite being 15 years of age.				

Long-Term Phase 3 Safety Studies				
Study	**Description**	**Patients [actual age]**	**Regimen**	**N†**
96-0-025 [US] [R98-0213-506-C3-E]	Open label, single concentration, long-term, multicenter study	Children with moderate or severe atopic dermatitis [aged 2-15 years]	Tacrolimus (0.1%) ointment twice daily for up to 1 year	255
FG-06-12 [Europe] [FG98-506-07]	Open label, single concentration, long-term, multicenter study	Adults with moderate or severe atopic dermatitis [aged 18-70 years]	Tacrolimus (0.1%) ointment twice daily for up to 1 year	318‡
† Number of patients who received at least one dose of study drug. ‡ Two patients did not have data beyond baseline and were excluded from safety analyses.				

Controlled Studies Conducted in Japan				
Protocol Number	**Study Design**	**Patient Population [actual age]**	**Regimen**	**No. Treated ‡‡ (treatment group)**
FJ-103 Phase 2 [1999000229-JP]	Single (patient) blind, intrasubject comparative study	Patients with AD [aged 16-58 years]	0.03%, 0.1%, or 0.3% tacrolimus ointment (one side) and vehicle (other side), 100 cm^2 area, twice daily; for 1 week (oozing lesions); for 3 weeks (lichenified lesions)	52 18 (0.03%) 18 (0.1%) 16 (0.3%)
FJ-104 Phase 2 [1999000130-JP]	Double-blind, randomized, parallel group study	Adult patients with acute-type AD [aged 16-61 years]	0.03%, 0.1%, or 0.3% tacrolimus ointment twice daily for 1 week, ≤100 cm^2 area	151 49 (0.03%) 51 (0.1%) 51 (0.3%)
FJ-105 Phase 2 [1999000130-JP]	Double-blind, randomized, parallel group study	Adult patients with chronic-type AD [aged 16-56 years]	0.1%, 0.3%, or 0.5% tacrolimus ointment or 0.12% betamethasone valerate (BV) twice daily for 3 weeks, ≤100 cm^2 area	190 50 (0.1%) 46 (0.3%) 48 (0.5%) 46 (BV)
FJ-107 Phase 2 [R98-0198-506-C2-E]	Double-blind, randomized, parallel group study	Adult patients with chronic-type AD on the trunk/ extremities [aged 16-62 years]	0.03% or 0.1% tacrolimus ointment or vehicle twice daily for 3 weeks, ≤100 cm^2 area	211 70 (0.03%) 69 (0.1%) 72 (Veh)
FJ-108 Phase 3 [R98-0103-506-C3-E]	Randomized parallel group comparative study	Adult AD patients with disease affecting the trunk/ extremities [aged 16-53 years]	0.1% tacrolimus ointment or 0.12% betamethasone valerate (BV) twice daily for 3 weeks	180 89 (0.1%) 91 (BV)
FJ-109 Phase 3 [R98-0104-506-C3-E]	Randomized parallel group comparative study	Adult AD patients with disease affecting the face/neck [aged 16-70 years]	0.1% tacrolimus ointment or 0.1% alclometasone dipropionate (AL) twice daily for 1 week	151 75 (0.1%) 76 (AL)
AD: atopic dermatitis. BV: 0.12% betamethasone valerate. AL: alclometasone dipropionate. Veh: vehicle. ‡‡ Number of patients who received at least one dose of study drug. Twelve of these patients, five in FJ-103, two in FJ-104, one in FJ-105, one in FJ-108, one in FJ-111, and two in FG-06-12, were NOT considered safety evaluable and were not included in safety analyses.				

Uncontrolled Studies Conducted in Japan				
Protocol Number	**Study Design**	**Patient Population [actual age]**	**Regimen**	**No. Treated ‡‡**
FJ-111 Phase 3 [R98-0229-506-C2-E]	Open-label, single concentration, long-term multicenter study	Adult AD patients [aged 16-65 years]	0.1% tacrolimus ointment once or twice daily for up to 2 years§§	569
FJ-110§ Phase 3 [R98-0151-506-C3-E]	Open-label, long-term observation study	Adult AD patients with disease affecting the face/neck [aged 18-70 years]	0.1% tacrolimus ointment once or twice daily for 6 weeks	62
AD: atopic dermatitis. ‡‡ Number of patients who received at least one dose of study drug. § Study FJ-110 is an extension study of FJ-109; patients were enrolled in the FJ-109 0.1% tacrolimus ointment treatment group. Both FJ-109 and FJ-110 were conducted in patients with facial/neck lesions. §§ Ongoing study;1-year data available.				

Supportive Phase 2 Studies				
Protocol Number	**Study Design**	**Patient Population [actual age]**	**Regimen**	**No. Treated ‡‡ (treatment group)**
95-0-003† Phase 2 [R97-0001-506-C2-E]	Double-blind, randomized, dose response study	Children with moderate or severe AD [aged 6-16 years]	Tacrolimus (0.03%, 0.1%, or 0.3%) ointment or vehicle twice daily (maximum: 20 g ointment/day) for 3 weeks	180 43 (0.03%) 49 (0.1%) 44 (0.3%) 44 (Veh)
FG-06-01‡ Phase 2 [FG96-506-03]	Double-blind, randomized, parallel group, dose response study	Patients with AD [aged 13-63 years]	Tacrolimus (0.03%, 0.1%, or 0.3%) ointment or vehicle twice daily for 3 weeks; 200 to 1000 cm^2 area selected at baseline for treatment.	213 54 (0.03%) 54 (0.1%) 51 (0.3%) 54 (Veh)
95-0-009† Phase 2 [R97-0067-506-C2-E]	Double blind, randomized, sequential group, dose-escalation study	Children with moderate or severe AD [aged 3-6 years]	Tacrolimus (0.03% or 0.1%) ointment or vehicle twice daily for up to 3 weeks	33 12 (0.03%), 13 (0.1%) 8 (Veh)
95-0-013† Phase 2 [R97-0061-506-C2-E]	Double blind, randomized, sequential group, dose-escalation study	Adults with moderate or severe AD [aged 17-69 years]	Tacrolimus (0.03%, 0.1%, or 0.3%) ointment or vehicle twice daily for up to 3 weeks	26 7 (0.03%) 6 (0.1%) 7 (0.3%) 6 (Veh)
AD: atopic dermatitis. Veh: vehicle. † United States. ‡ Europe. ‡‡ Number of patients who received at least one dose of study drug.				

2 JAPANESE EXPERIENCE

2.1 Controlled Clinical Studies

Six controlled studies were conducted in Japan (Studies FJ-103, FJ-104, FJ-105, FJ-107, FJ-108, and FJ-109). Efficacy results for these studies are summarized in Table 1. Moderate improvement was observed for more than 70% of tacrolimus-treated patients in each study. Irritation at the application site (i.e., skin burning, flushing, and pruritus) was common, but few patients discontinued tacrolimus ointment due to this adverse event, and skin irritation tended to decrease over time with clinical improvement. Nonapplication site adverse events were uncommon.

Of special note, Study FJ-109 was conducted in patients with facial/neck lesions. In this study, 0.1% tacrolimus ointment was associated with significantly better efficacy for the short-term (1 week) treatment of the face and neck than alclometasone dipropionate *[Note: alclometasone dipropionate is a medium to low potency steroid widely used in Japan; the short duration of this study was partially to minimize the potential for adverse effects of the steroid comparator]*. A total of 86% of tacrolimus ointment-treated patients compared with 36% alclometasone dipropionate-treated patients had a global improvement rating of *cured or markedly improved ($p<0.001$, chi-squared test)*. Improvement in facial erythema, swelling, papule/serous papule/phlyctenule, lichenification and itching was more rapid in the tacrolimus ointment group.

Table 1: Improvement Rate† for Tacrolimus Ointment in Atopic Dermatitis: Japanese Experience, Controlled Clinical Studies

Study Protocol	Final Global Improvement Rating (%)				
	Tac 0.03%	Tac 0.1%	BV (0.12%)	AL (0.1%)	Vehicle Control
FJ-103 §	16/17 (94)*	17/17 (100)*	----	----	24/34 (70.6)‡
FJ-104 §	47/48 (98)	49/50 (98)	----	----	----
FJ-105 §	----	41/41 (100)	29/40 (72)	----	----
FJ-107	48/67 (72)**	57/62 (92)**	----	----	31/63 (49)
FJ-108	----	73/78 (94)	76/84 (90)	----	----
FJ-109	----	71/73 (97)††	----	49/70 (70)††	----

Tac = Tacrolimus ointment; BV = Betamethasone valerate ointment; AL = Alclometasone dipropionate ointment.
† Improvement Rating = *Moderate* or better improvement in skin findings of the Final Global Improvement Rating.
‡Each treated patient served as his/her own control by having a second identical lesion treated with vehicle ointment.
§ Included a 0.3% and/or a 0.5% tacrolimus arm; these concentrations are not under clinical development.
*$p<0.01$, tacrolimus ointment vs. ointment base, Wilcoxon matched-pair signed-rank test.
**$p<0.01$, Dunnett's type multiple comparison vs. ointment base.
†† Statistical analyses were not performed for moderate improvement; tacrolimus ointment had a statistically higher incidence of *at least marked improvement* (63/73, 86%) compared with alclometasone dipropionate (25/70, 36%; $p<0.001$, chi-squared test).
Source: Study Reports 1999000229-JP, 1999000130-JP, R98-0198-506-C2-E, R98-0103-506-C3-E, and R98-0104-506-C3-E.

2.2 Uncontrolled Clinical Studies

Two open-label studies were conducted in Japan, a 2-year study (Study FJ-111, 1-year data available, n=569) and a 6-week extension of FJ-109 (Study FJ-110, n=62). The 0.1% tacrolimus ointment concentration was evaluated in these studies.

A global improvement rating of moderate improvement or better was observed in 240/265 (91%) of patients in Study FJ-111 at 52 weeks and 54/54 (100%) of patients in Study FJ-110 at 6 weeks.

Irritation at the application site (e.g., pruritus, flushing, tingling, and burning) occurred in 450/568 (79%) patients in FJ-111 and 3/62 (5%) patients in FJ-110. The incidence of these events in the 6-week extension Study FJ-110 was much lower than that observed with 1 week of treatment in its primary study (Study FJ-109).

In FJ-111, 53% (300/568) of atopic dermatitis patients entered the study with skin disorders associated with previous therapy (e.g., skin atrophy, capillary vasodilatation, rosacea-like dermatitis/perioral dermatitis-like findings). By the end of 1 year on study, the incidence of each of these disorders was reduced by approximately half and the severity of these symptoms was substantially ameliorated for most patients. In extension Study FJ-110, there was no evidence of tacrolimus ointment-associated skin atrophy, rosacea-like dermatitis or capillary vasodilatation after a total of 7 weeks of once- or twice-daily application to the face.

2.3 Phase 2 Studies

Four vehicle-controlled Phase 2 studies provide primary supportive evidence of the efficacy of tacrolimus ointment (Studies 95-0-003, 95-0-009, 95-0-013 and FG-06-01).

Improvement in clinical status based on the Physician's Global Evaluation of Clinical Response in the US Phase 2 studies is summarized in Table 2. In Study FG-06-01, 91% (49/54) of intent-to-treat patients in the 0.1% tacrolimus ointment group and 81% (44/54) of those in the 0.03% tacrolimus ointment group compared with 20% (11/54) of those in the vehicle group demonstrated at least moderate improvement (moderately improved, markedly improved or completely resolved) based on the Physician's Global Assessment of the Treated Area at the end of the treatment period.

Table 2: Improvement Based on Physician's Global Evaluation of Clinical Response in the Supportive US Phase 2 Studies

	Improvement	Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
All Studies (95-0-003, 95-0-009, 95-0-013)	≥90%	12/58 (20.7%)	28/62 (45.2%)	29/68 (42.6%)
	≥75%	17/58 (29.3%)	37/62 (59.7%)	43/68 (63.2%)
	≥50%	22/58 (37.9%)	47/62 (75.8%)	56/68 (82.4%)
Pediatric Studies (95-0-003, 95-0-009)	≥90%	12/52 (23.1%)	28/55 (50.9%)	26/62 (41.9%)
	≥75%	17/52 (32.7%)	37/55 (67.3%)	37/62 (59.7%)
	≥50%	22/52 (42.3%)	45/55 (81.8%)	50/62 (80.6%)
Adult Study (95-0-013)	≥90%	0/6 (0%)	0/7 (0%)	3/6 (50.0%)
	≥75%	0/6 (0%)	0/7 (0%)	6/6 (100.0%)
	≥50%	0/6 (0%)	2/7 (28.6%)	6/6 (100.0%)

Patient population: Modified intent-to-treat (MITT); all randomized patients who received at least one dose of study drug. Study FG-06-01, conducted in Europe, rated improvement using a rating scale which differed from that used in the US Phase 2 studies in that the percentage improvement range was not predefined by the protocol for marked or moderate improvement and the scale lacked the Excellent Improvement category; therefore the European Phase 2 results were not combined with the US Phase 2 results for this table. ≥75% improvement = at least Marked improvement from baseline at the end of treatment. ≥50% improvement = at least Moderate improvement from baseline at the end of treatment.
Source: Study Reports R97-0001-506-C2-E (Appendix Table B.6.1.2, Listing D.4), R97-0067-506-C2-E (Appendix Table B.6.1, Listing D.4), and R97-0061-506-C2-E (Appendix Table B.6.1, Listing D.4).

Appendix III

Patient Disposition, Demographics and Other Baseline Characteristics, and Ointment Administration Data for Each of the Three 12-Week, Double-Blind Studies

Study 97-0-037, Pediatric Study

A total of 489 patients were screened for enrollment in this study, of whom 352 were enrolled at 23 sites. The most common reasons for screening failure were lack of involvement of at least 10% total body surface area and lack of moderate to severe atopic dermatitis. All enrolled patients except one received at least one dose of study drug and were included in the intent-to-treat population. Patient No. 11703 (vehicle) was randomized but withdrew consent prior to receiving a dose of study drug.

Patient Population (Study 97-0-037)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized	117	117	118	352
Intent-to-Treat	116 (99.1%)	117 (100.0%)	118 (100.0%)	351 (99.7%)
2-6 years of age	*72*	*74*	*69*	*215*
7-15 years of age	*44*	*43*	*49*	*136*

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug). Source: Study Report R98-0214-506-C3-E, Tables 13.1.1 and Appendix 14.3.2.1.1.

Patient Disposition (Study 97-0-037)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Intent to Treat	116	117	118	351
Completed Treatment	51 (44.0%)	94 (80.3%)	101 (85.6%)	246 (70.1%)
Discontinued Treatment	65 (56.0%)	23 (19.7%)	17 (14.4%)	105 (29.9%)
Lack of Efficacy	46 (39.7%)	4 (3.4%)	5 (4.2%)	55 (15.7%)
Adverse Event	9 (7.8%)	6 (5.1%)	3 (2.5%)	18 (5.1%)
Application Site	9	2	2	13
Nonapplication Site	0	4	1	5
Administrative Reason†	10 (8.6%)	13 (11.1%)	9 (7.6%)	32 (9.1%)
Discontinuation Day‡				
Mean ± SD	22.4 ± 20.0	30.4 ± 26.6	21.4 ± 16.1	
Median	21	23	22	

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
† Administrative reasons included noncompliance, lost to follow-up, patient refusal, patient moved out of state, and patient given wrong study medication (Study Report R98-0214-506-C3-E, Appendix 14.4.1.1.1).
‡ For patients who discontinued.
SD: standard deviation.
Source: Study Report R98-0214-506-C3-E, Tables 13.1.2, 13.1.3, and 13.5.8, and Appendix 14.4.1.1.1.

Baseline Demographics and Patient Characteristics (Study 97-0-037)

Variable		Treatment Group			Total	p-Value
		Vehicle	Concentration of Tacrolimus Ointment			
			0.03%	0.1%		
Total Number of Patients		116	117	118	351	
Gender	Female	63 (54.3%)	62 (53.0%)	61 (51.7%)	186 (53.0%)	0.923
	2-6 years	36 (50.0%)	36 (48.6%)	36 (52.2%)	108 (50.2%)	
	7-15 years	27 (61.4%)	26 (60.5%)	25 (51.0%)	78 (57.4%)	
	Male	53 (45.7%)	55 (47.0%)	57 (48.3%)	165 (47.0%)	
	2-6 years	36 (50.0%)	38 (51.4%)	33 (47.8%)	107 (49.8%)	
	7-15 years	17 (38.6%)	17 (39.5%)	24 (49.0%)	58 (42.6%)	
Race	White	78 (67.2%)	76 (65.0%)	75 (63.6%)	229 (65.2%)	0.976
	Black	28 (24.1%)	32 (27.4%)	34 (28.8%)	94 (26.8%)	
	Oriental	8 (6.9%)	7 (6.0%)	6 (5.1%)	21 (6.0%)	
	Other	2 (1.7%)	2 (1.7%)	3 (2.5%)	7 (2.0%)	
Ethnicity	Nonhispanic	107 (92.2%)	112 (95.7%)	112 (94.9%)	331 (94.3%)	0.486
	Hispanic	9 (7.8%)	5 (4.3%)	6 (5.1%)	20 (5.7%)	
Age (yrs)	Mean ± SD	5.8 ± 3.3	6.1 ± 3.8	6.4 ± 3.7	6.1 ± 3.6	0.408
	Median	5	5	6	5	
	Range	2 - 15	2 - 15	2 - 15	2 - 15	
Severity	Moderate	47 (40.5%)	45 (38.5%)	43 (36.4%)	135 (38.5%)	0.814
	2-6 years	27 (37.5%)	26 (35.1%)	22 (31.9%)	75 (34.9%)	
	7-15 years	20 (45.5%)	19 (44.2%)	21 (42.9%)	60 (44.1%)	
	Severe	69 (59.5%)	72 (61.5%)	75 (63.6%)	216 (61.5%)	
	2-6 years	45 (62.5%)	48 (64.9%)	47 (68.1%)	140 (65.1%)	
	7-15 years	24 (54.5%)	24 (55.8%)	28 (57.1%)	76 (55.9%)	

Table continued on next page

Baseline Demographics and Patient Characteristics (Study 97-0-037) (continued)

Variable	Treatment Group			Total	p-Value
	Vehicle	Concentration of Tacrolimus Ointment			
		0.03%	0.1%		
Total Number of Patients	116	117	118	351	
% BSA Mean ± SD	49.2 ± 28.8	45.6 ± 27.5	48.3 ± 24.8	47.7 ± 27.1	0.570
Affected					
2-6 years					
≥10% to 25%	48.1 ± 28.8	46.2 ± 27.9	51.1 ± 23.9	48.4 ± 26.9	0.561
≥25% to 50%	22 (30.6%)	25 (33.8%)	11 (15.9%)	58 (27.0%)	
≥50% to 75%	18 (25.0%)	16 (21.6%)	23 (33.3%)	57 (26.5%)	0.254
≥75% to 100%	16 (22.2%)	19 (25.7%)	21 (30.4%)	56 (26.0%)	
	16 (22.2%)	14 (18.9%)	14 (20.3%)	44 (20.5%)	
7-15 years	51.0 ± 29.2	44.5 ± 27.2	44.4 ± 25.9	46.6 ± 27.4	0.430
≥10% to 25%	11 (25.0%)	16 (37.2%)	16 (32.7%)	43 (31.6%)	
≥25% to 50%	12 (27.3%)	1 (25.6%)	13 (26.5%)	36 (26.5%)	0.696
≥50% to 75%	9 (20.5%)	9 (20.9%)	13 (26.5%)	31 (22.8%)	
≥75% to 100%	12 (27.3%)	7 (16.3%)	7 (14.3%)	26 (19.1%)	
Head/Neck	100 (86.2%)	100 (85.5%)	93 (78.8%)	293 (83.5%)	0.266
Affected 2-6 years	64 (88.9%)	62 (83.8%)	56 (81.2%)	182 (84.7%)	0.441
7-15 years	36 (81.8%)	38 (88.4%)	37 (75.5%)	111 (81.6%)	0.289

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
SD: standard deviation.
BSA: total body surface area. Severity: Rajka & Langeland criteria. P-value from chi-square test for discrete variables and one-way ANOVA with treatment as source of variation for continuous variables; for % BSA affected, p-value is for individual age group rather than overall due to age adjustment in the calculation.
Source: Study Report R98-0214-506-C3-E, Tables 14.3.2.1.1, 14.3.2.1.2, 14.3.2.2.1, 14.3.2.2.2, 14.3.2.3.1, 14.3.2.3.2.

Ointment Administration (All Patients, Study 97-0-037)

Variable		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Total Number of Patients		116	117	118
Percent BSA Treated at Start of Therapy	N	116	117	118
	Mean ± SD	48.7 ± 28.1	45.5 ± 27.5	48.1 ± 24.7
	Median	41.8	39.0	48.5
	Range	10.0 - 98.4	10.0 - 100.0	10.0 - 97.6
Treatment Period Days	N	116	117	118
	Mean ± SD	49.1 ± 34.7	72.3 ± 27.0	73.6 ± 26.5
	Median	46.5	85.0	85.0
	Range	1 - 93	1 - 133	1 - 134
Total Grams of Ointment Used	N	95	92	90
	Mean ± SD	282.5 ± 353.0	319.3 ± 328.6	295.4 ± 268.8
	Median	190.0	236.9	220.0
	Range	4 - 2201	7 - 1973	2 - 1580
Grams of Ointment Per Day	N	95	92	90
	Mean ± SD	7.4 ± 6.3	4.6 ± 4.4	4.1 ± 3.5
	Median	4.8	3.2	3.3
	Range	0.7 - 26.5	0.4 - 21.7	0.5 - 20.4
Total Milligrams Tacrolimus Applied	N	N/A	92	90
	Mean ± SD		95.8 ± 98.6	295.4 ± 268.8
	Median		71.1	220.0
	Range		2.1 - 591.9	2 - 1580

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
BSA: total body surface area. SD: standard deviation. N/A: not applicable.
Source: Study Report R98-0214-506-C3-E, Table 13.3.1.1 and Appendix 14.3.2.2.1.

Ointment Administration (By Age, Study 97-0-037)

Variable		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
2-6 years of age				
Percent BSA Treated at Start of Therapy	N	72	74	69
	Mean ± SD	47.5 ± 27.9	46.1 ± 27.9	50.7 ± 23.6
	Median (Range)	39.8 (10.0 - 98.4)	44.3 (10.0 - 100.0)	51.0 (10.0 - 91.5)
Treatment Period Days	N	72	74	69
	Mean ± SD	50.6 ± 35.5	72.3 ± 26.8	72.0 ± 28.1
	Median (Range)	63.5 (1 - 92)	85.0 (1 - 133)	84.0 (1 - 134)
Grams of Ointment Per Day	N	61	58	52
	Mean ± SD	6.7 ± 5.3	4.2 ± 3.5	3.9 ± 3.3
	Median (Range)	4.6 (0.8 - 22.4)	3.2 (0.4 - 15.8)	3.0 (0.5 - 20.4)
Total Grams of Ointment Used	N	61	58	52
	Mean ± SD	268.7 ± 302.5	304.0 ± 264.3	253.5 ± 173.3
	Median (Range)	209 (4 - 1555)	228.5 (7 - 1135)	218.5 (2 - 827)
Total Milligrams Tacrolimus Applied	N		58	52
	Mean ± SD	N/A	91.2 ± 79.3	253.5 ± 173.3
	Median (Range)		68.6 (2.1 - 340.5)	218.5 (2 - 827)
7-15 years of age				
Percent BSA Treated at Start of Therapy	N	44	43	49
	Mean ± SD	50.7 ± 28.8	44.4 ± 27.0	44.3 ± 25.9
	Median (Range)	45.8 (10.5 - 96.5)	35.0 (12.0 - 98.3)	40.0 (10.3 - 97.6)
Treatment Period Days	N	44	43	49
	Mean ± SD	46.6 ± 33.6	72.3 ± 27.5	76.0 ± 24.1
	Median (Range)	25.5 (2 - 93)	85.0 (1 - 94)	85.0 (7 - 99)
Grams of Ointment Per Day	N	34	34	38
	Mean ± SD	8.6 ± 7.9	5.2 ± 5.6	4.4 ± 3.8
	Median (Range)	6.0 (0.7 - 26.5)	3.5 (0.4 - 21.7)	3.6 (0.6 - 17.4)
Total Grams of Ointment Used	N	34	34	38
	Mean ± SD	307.1 ± 433.1	345.4 ± 419.5	352.8 ± 355.7
	Median (Range)	152.5 (17 - 2201)	252.4 (15 - 1973)	237.0 (5.9 - 1580)
Total Milligrams Tacrolimus Applied	N		34	38
	Mean ± SD	N/A	103.6 ± 125.8	352.8 ± 355.7
	Median (Range)		75.7 (4.5 - 591.9)	237.0 (5.9 - 1580)

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
BSA: total body surface area. SD: standard deviation. N/A: not applicable.
Source: Study Report R98-0214-506-C3-E, Table 13.3.1.2 and Appendix 14.3.2.2.2.

Study 97-0-035, Adult Study

A total of 489 patients were screened for enrollment in this study, of whom 305 were enrolled at 21 sites. The most common reasons for screening failure were lack of moderate to severe atopic dermatitis and lack of involvement of at least 10% of total body surface area. A total of 304 enrolled patients received at least one dose of study drug and were included in the intent-to-treat population (ITT). Patient No. 19514 was randomized but was not dispensed study drug due to postrandomization discovery of pregnancy (Study Report L1999000006, Appendix 14.4.1.1.2).

Patient Population (Study 97-0-035)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized	103	103	99	305
Intent-to-Treat	102 (99.0%)	103 (100.0%)	99 (100.0%)	304 (99.7%)

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug). Source: Study Report L1999000006, Table 13.1.1.

Patient Disposition (Study 97-0-035)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Intent to Treat	102	103	99	304
Completed Treatment	38 (37.3%)	73 (70.9%)	71 (71.7%)	182 (59.9%)
Discontinued Treatment	64 (62.7%)	30 (29.1%)	28 (28.3%)	122 (40.1%)
Lack of Efficacy	41 (40.2%)	11 (10.7%)	10 (10.1%)	62 (20.4%)
Adverse Event	12# (11.8%)	5# (4.9%)	7 (7.1%)	24 (7.9%)
Application Site	9	3	5	17
Nonapplication Site	3#	2#	2	7
Administrative Reason†	11 (10.8%)	14 (13.6%)	11 (11.1%)	36 (11.8%)
Discontinuation Day‡				
Mean ± SD	20.6 ± 17.9	35.9 ± 23.9	27.8 ± 22.9	
Median	15.0	30.0	22.0	

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug). SD=standard deviation.
† Administrative reasons included lost to follow-up, patient refusal, noncompliance, pregnancy, and patient enrolled but did not meet inclusion criteria (Study Report L1999000006, Appendix 14.4.1.1.1).
‡ For patients who discontinued.
# As an administrative convention, pregnancies were recorded as nonapplication site adverse events. Therefore, two patients (Patient Nos. 155501 and 159519) who became pregnant appear in source Table 13.5.8 as discontinuing due to an adverse event. However, these patients were considered to have discontinued for an administrative reason, not a nonapplication site adverse event, here and for source Table 13.1.2.
Source: Study Report L1999000006, Tables 13.1.2, 13.1.3, 13.5.8, and Appendices 14.4.1.1.1 and 14.4.4.1.

Baseline Demographics and Patient Characteristics (Study 97-0-035)

Variable	Treatment Group			Total	p-Value
	Vehicle	Concentration of Tacrolimus Ointment			
		0.03%	0.1%		
Total # of Patients	102	103	99	304	
Gender					
Female	52 (51.0%)	62 (60.2%)	61 (61.6%)	175 (57.6%)	0.251
Male	50 (49.0%)	41 (39.8%)	38 (38.4%)	129 (42.4%)	
Race					
White	67 (65.7%)	69 (67.0%)	66 (66.7%)	202 (66.4%)	0.908
Black	30 (29.4%)	28 (27.2%)	26 (26.3%)	84 (27.6%)	
Oriental	3 (2.9%)	5 (4.9%)	5 (5.1%)	13 (4.3%)	
American Indian	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	
Other	1 (1.0%)	1 (1.0%)	2 (2.0%)	4 (1.3%)	
Ethnicity					
Nonhispanic	99 (97.1%)	101 (98.1%)	93 (3.9%)	293 (96.4%)	0.265
Hispanic	3 (2.9%)	2 (1.9%)	6 (6.1%)	11 (3.6%)	
Age (yrs)					
Mean ± SD	38.6 ± 13.8	38.0 ± 13.8	39.3 ± 13.0	38.6 ± 13.5	0.786
Median	36	37	38	37	
Range	16 - 75	15 - 72	17 - 77	15 - 77	
Severity					
Moderate	49 (48.0%)	54 (52.4%)	39 (39.4%)	142 (46.7%)	0.169
Severe	53 (52.0%)	49 (47.6%)	60 (60.6%)	162 (53.3%)	
% BSA Affected					
Mean ± SD	43.4 ± 24.5	41.4 ± 25.1	42.4 ± 26.7	42.4 ± 25.4	0.852
Median	37.3	35	33	35	
Range	11.2 – 98	10 – 100	10 – 100	10 – 100	
≥10% to 25%	34 (33.3%)	36 (35.0%)	33 (33.3%)	103 (33.9%)	0.962
≥25% to 50%	33 (32.4%)	33 (32.0%)	31 (31.3%)	97 (31.9%)	
≥50% to 75%	18 (17.6%)	21 (20.4%)	17 (17.2%)	56 (18.4%)	
≥75% to 100%	17 (16.7%)	13 (12.6%)	18 (18.2%)	48 (15.8%)	
Head/Neck Affected	91 (89.2%)	82 (79.6%)	79 (79.8%)	252 (82.9%)	0.106

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
SD=standard deviation. BSA=total body surface area. Severity: Rajka & Langeland criteria.
P-value from chi-squared test for discrete variables except for Head/Neck Affected (Fisher's exact test), and one-way ANOVA with treatment as source of variation for continuous variables.
Source: Study Report L1999000006, Tables 14.3.2.1, 14.3.2.2, 14.3.2.3.

Ointment Administration (Study 97-0-035)

Variable		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Total Number of Patients		102	103	99
Percent BSA Treated at Start of Therapy	N	102	103	99
	Mean ± SD	43.4 ± 24.5	41.3 ± 25.0	42.4 ± 26.8
	Median	37.3	35.0	33.0
	Range	11.2 - 98.0	10.0 - 100.0	10.0 - 100.0
Treatment Period Days	N	102	103	97
	Mean ± SD	44.9 ± 34.9	70.1 ± 26.3	67.2 ± 29.6
	Median	33.0	84.0	84.0
	Range	1 - 117	1 - 100	1 - 96
Total Grams of Ointment Used	N	87	85	76
	Mean ± SD	294.9 ± 339.0	431.9 ± 484.1	387.5 ± 410.8
	Median	166.0	268.0	242.0
	Range	3.0 - 2069.0	2.0 - 2816.0	1.0 - 1951.0
Grams of Ointment Per Treatment Period Day	N	87	85	76
	Mean ± SD	9.1 ± 10.6	6.0 ± 5.9	5.6 ± 5.0
	Median	5.4	3.9	4.4
	Range	0.9 - 70.7	0.3 - 33.1	0.3 - 22.7
Total Milligrams Tacrolimus Applied	N	N/A	85	76
	Mean ± SD		129.6 ± 145.2	387.5 ± 410.8
	Median		80.4	242.0
	Range		0.6 - 844.8	1.0 - 1951.0

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug). Only patients who returned all tubes at all visits are included for ointment/tacrolimus used.
BSA=total body surface area. SD=standard deviation. N/A=not applicable.
Source: Study Report L1999000006, Table 13.3.1 and Appendix 14.3.2.2.

Study 97-0-036, Adult Study

A total of 493 patients were screened for enrollment in this study, of whom 328 were enrolled at 20 sites. The most common reasons for screening failure were lack of involvement of at least 10% total body surface area and lack of moderate to severe atopic dermatitis. All 328 enrolled patients were dispensed study drug, received at least one dose of study drug, and were included in the intent-to-treat population.

Patient Population (Study 97-0-036)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized	110	108	110	328
Intent-to-Treat	110 (100.0%)	108 (100.0%)	110 (100.0%)	328 (100.0%)

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
Source: Study Report L1999000008, Table 13.1.1.

Patient Disposition (Study 97-0-036)

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Intent to Treat	110	108	110	328
Completed Treatment	29 (26.4%)	77 (71.3%)	86 (78.2%)	192 (58.5%)
Discontinued Treatment	81 (73.6%)	31 (28.7%)	24 (21.8%)	136 (41.5%)
Lack of Efficacy	54 (49.1%)	15 (13.9%)	8 (7.3%)	77 (23.5%)
Adverse Event	14 (12.7%)	8 (7.4%)	4# (3.6%)	26# (7.9%)
Application Site	14	8	4	26
Nonapplication Site¶	2	0	1#	3#
Administrative Reason†	13 (11.8%)	8 (7.4%)	12 (10.9%)	33 (10.1%)
Discontinuation Day‡				
Mean ± SD	18.0 ± 18.1	36.6 ± 25.1	20.5 ± 19.9	
Median	13	36	15	

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
SD: standard deviation.
¶ Three patients (Patient Nos. 154601 and 245615, vehicle; Patient No. 232607, 0.1% tacrolimus) discontinued as a result of both application and nonapplication site adverse events.
† Administrative reasons included lost to follow-up, patient refusal, noncompliance, pregnancy, site error, and patient enrolled but did not meet entrance criteria (Study Report L1999000008, Appendix 14.4.1.1).
‡ For patients who discontinued. # As an administrative convention, pregnancies were recorded as nonapplication site adverse events. Therefore, two patients (Patient Nos. 42602 and 220607) who became pregnant appear in source Table 13.5.8 as discontinuing due to an adverse event. However, these patients were considered to have discontinued due to an administrative reason, not a nonapplication site adverse event here and for source Table 13.1.2.
Source: Study Report L1999000008, Tables 13.1.2, 13.1.3, 13.5.8, and Appendices 14.4.1.1 and 14.4.4.1.

Baseline Demographics and Patient Characteristics (Study 97-0-036)

Variable	Treatment Group			Total	p-Value
	Vehicle	Concentration of Tacrolimus Ointment			
		0.03%	0.1%		
Total # of Patients	110	108	110	328	
Gender					
Female	65 (59.1%)	54 (50.0%)	63 (57.3%)	182 (55.5%)	0.361
Male	45 (40.9%)	54 (50.0%)	47 (42.7%)	146 (44.5%)	
Race					
White	73 (66.4%)	75 (69.4%)	73 (66.4%)	221 (67.4%)	0.928
Black	27 (24.5%)	27 (25.0%)	29 (26.4%)	83 (25.3%)	
Oriental	7 (6.4%)	4 (3.7%)	7 (6.4%)	18 (5.5%)	
American Indian	1 (0.9%)	1 (0.9%)	1 (0.9%)	3 (0.9%)	
Other	2 (1.8%)	1 (0.9%)	0 (0.0%)	3 (0.9%)	
Ethnicity					
Nonhispanic	108 (98.2%)	107 (99.1%)	105 (95.5%)	320 (97.6%)	0.195
Hispanic	2 (1.8%)	1 (0.9%)	5 (4.5%)	8 (2.4%)	
Age (yrs)					
Mean ± SD	38.5 ± 14.3	37.9 ± 13.8	39.2 ± 15.8	38.5 ± 14.6	0.793
Median	39	37	39	38	
Range	16 - 73	16 - 76	16 -79	16 -79	
Severity					
Moderate	49 (44.5%)	39 (36.1%)	47 (42.7%)	135 (41.2%)	0.413
Severe	61 (55.5%)	69 (63.9%)	63 (57.3%)	193 (58.8%)	
% BSA Affected					
Mean ± SD	47.4 ± 26.7	48.2 ± 28	47.2 ± 27.2	47.6 ± 27.2	0.956
Median	43.8	42.3	43.3	42.8	
Range	10 – 98.6	10 –100	10 – 100	10 – 100	
≥10% to 25%	28 (25.5%)	30 (27.8%)	32 (29.1%)	90 (27.4%)	0.994
≥25% to 50%	35 (31.8%)	31 (28.7%)	31 (28.2%)	97 (29.6%)	
≥50% to 75%	23 (20.9%)	21 (19.4%)	22 (20.0%)	66 (20.1%)	
≥75% to 100%	24 (21.8%)	26 (24.1%)	25 (22.7%)	75 (22.9%)	
Head/Neck Affected	98 (89.1%)	100 (92.6%)	100 (90.9%)	298 (90.9%)	0.681

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug).
SD=standard deviation. BSA=total body surface area. Severity: Rajka & Langeland criteria.
P-value from chi-squared test for discrete variables except for Head/Neck Affected (Fisher's exact test), and one-way ANOVA with treatment as source of variation for continuous variables.
Source: Study Report L1999000008, Tables 14.3.2.1, 14.3.2.2, 14.3.2.3.

Ointment Administration (Study 97-0-036)

Variable		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Total Number of Patients		110	108	110
Percent BSA Treated at Start of Therapy	N	110	108	110
	Mean ± SD	47.2 ± 26.6	48.1 ± 27.9	47.0 ± 27.1
	Median	43.3	42.3	43.3
	Range	10.0 - 98.6	10.0 - 100.0	10.0 - 100.0
Treatment Period Days	N	110	108	110
	Mean ± SD	35.5 ± 33.6	68.8 ± 27.2	68.8 ± 29.9
	Median	20	84	85
	Range	1 - 118	1 - 102	1 - 101
Total Grams of Ointment Used	N	92	87	83
	Mean ± SD	239.5 ± 273.3	396.0 ± 324.1	496.5 ± 510.3
	Median	151.9	324.0	340.0
	Range	5.0 - 1511.0	0.0† - 1596.0	4.0 - 2497.0
Grams of Ointment Per Treatment Period Day	N	92	87	83
	Mean ± SD	10.0 ± 9.4	6.3 ± 5.0	7.2 ± 6.3
	Median	6.8	5.6	5.1
	Range	0.9 - 44.9	0.0† - 25.1	0.5 - 29.4
Total Milligrams Tacrolimus Applied	N	N/A	87	83
	Mean ± SD		118.8 ± 97.2	496.5 ± 510.3
	Median		97.2	340.0
	Range		0.0† - 478.8	4.0 - 2497.0

Intent-to-treat population : all randomized patients who were dispensed study drug (= received at least one dose of study drug). Only patients who returned all tubes at all visits are included for ointment/tacrolimus used.
BSA: total body surface area. SD: standard deviation. N/A: not applicable.
† Patient No. 14607 was treated for 2 days; however, the difference in tube weight (dispensed-returned) was recorded as 0.
Source: Study Report L1999000008, Table 13.3.1 and Appendix 14.3.2.2.

Appendix IV

Patient Selection Information for the Core Studies

Patient Selection Criteria for Each of the 12-Week Double-Blind Studies

Male and female patients were eligible for study participation if they met the following criteria at baseline/Day 1:

- a diagnosis of atopic dermatitis based on the Hanifin and Rajka Criteria
- moderate to severe atopic dermatitis based on the Rajka and Langeland grading system involving at least 10% of the body surface area
- at least 16 years of age [2-<16 years of age for the pediatric study]
- patient and parent/legal guardian, if applicable, provided written informed consent
- agreement by patient to protocol-specified washout requirements and concomitant therapy restrictions during the study including discontinuation of nonmedicated topical agents such as creams, lotions, and emollients (to treatment area); topical antihistamines; topical antimicrobials; topical, systemic or inhaled corticosteroids; non-sedating systemic antihistamines; light treatments (UVA, UVB); non-steroid immunosuppressants; and other investigational drugs
- if female, a negative pregnancy test; agreement by patient (all patients) to practice effective birth control
- agreement by patient or parent/legal guardian, if applicable, to comply with study requirements and to come to the clinic for required visits

Any of the following conditions resulted in exclusion from the study:

- skin disorder other than atopic dermatitis in the areas to be treated
- pigmentation, extensive scarring, or pigmented lesions in the proposed treatment areas which would interfere with the rating of efficacy parameters
- clinically infected atopic dermatitis at baseline

- anticipated requirement for systemic corticosteroids or more than 2 mg prednisone equivalent per day of inhaled and/or intranasal corticosteroids during the study
- known hypersensitivity to macrolides or any excipient of the ointment
- systemic disease, including cancer or history of cancer or human immunodeficiency virus (HIV) which would contraindicate the use of immunosuppressants
- chronic condition (e.g., diabetes, hypertension) which either is not stable or not well controlled
- pregnancy or breast feeding an infant
- previous enrollment in any atopic dermatitis study sponsored by Fujisawa

Washout Criteria

Pre-Study and Concomitant Therapy Restrictions	Washout Period Prior to Study	Restriction (Baseline Thru Week 12/End-of-Treatment)
Astemizole[1] Terfenadine[1] Other Non-Sedating Systemic Antihistamines[2]	6 weeks 7 days 7 days	Disallowed Disallowed Disallowed
Other investigational drugs	4 weeks	Disallowed
Non-steroidal immunosuppressants (e.g., cyclosporine methotrexate)	4 weeks	Disallowed
Light Treatments (UVA, UVB)	4 weeks	Disallowed
Systemic corticosteroids (PO and IV)	4 weeks	Disallowed
Intranasal and/or inhaled corticosteroids, if more than >2 mg prednisone equivalent required per day[3]	14 days[3]	Disallowed[3]
Topical corticosteroids	7 days	Disallowed
Topical H_1 and H_2 antihistamines	7 days	Disallowed
Topical antimicrobials	7 days	Disallowed
Other mediated topical agents[4]	7 days	Disallowed
Non-medicated topical agents (including creams, lotions, and emollients) in the areas to be treated with the randomized study ointment[5]	1 day	Disallowed in all areas being treated with the randomized study ointment[5]

1. Astemizole and Terfenadine are contraindicated with use of systemic tacrolimus.
2. Prohibited non-sedating antihistamines include, but are not limited to, cetirizine, loratidine, fexofenadine HCl, astemizole, and terfenadine. Sedating antihistamines, such as diphenhydramine may be used during the study if the patients are on a stable dose at baseline and remain on that dose during the study. The dosage of sedating antihistamines may be decreased or discontinued, but not increased during the study.
3. Intranasal and/or inhaled corticosteriods may be administered during the washout period and during the study only if the dosage required is less than or equal to 2 mg per day (prednisone equivalent).
4. Topical anesthetics may be used for required blood draws.
5. Non-medicated emollients may be used on areas not being treated with the randomized study ointment during the study.

Patient Selection Criteria for the Long-Term Pediatric Safety Study 96-0-025

Male and female patients were eligible for study participation if they met the following criteria:

- at least 2 years but less than 16 years of age
- a diagnosis of atopic dermatitis based on the Hanifin and Rajka Criteria
- moderate to severe atopic dermatitis based on the Rajka and Langeland grading system
- patient's parent or legal guardian had provided written informed consent
- patient had not used an investigational drug within 4 weeks of initiation of study drug administration
- agreement by patient and parent or legal guardian to discontinue use of systemic corticosteroids by the patient at study entry (if deemed necessary by the investigator, systemic corticosteroid therapy, limited to two courses or fewer, was permitted during the study)
- agreement by patient and parent or legal guardian to discontinue patient use of the following during the course of the study: creams and lotions, emollients (to treatment area), topical antihistamines, topical anti-infectives, topical corticosteroids, light treatments (e.g., UVA, UVB), and non-steroid immunosuppressants
- if female with child-bearing potential (A menstruating female), a negative pregnancy test and agreement to practice effective birth control during the study
- agreement by patient and parent or legal guardian to comply with study requirements and to come to the clinic for required visits

Any of the following conditions resulted in exclusion from the study:

- previous enrollment in any Fujisawa sponsored atopic dermatitis study
- serious skin disorder other than atopic dermatitis in the affected areas
- pigmentation or extensive scarring which would interfere with the rating of efficacy parameters
- clinically infected atopic dermatitis at study entry
- known hypersensitivity to macrolides or any excipient of the ointment
- systemic disease, including cancer or history of cancer or HIV which would contradict the use of tacrolimus
- chronic condition (e.g., diabetes) which is not stable and not well controlled
- likely requirement for systemic corticosteroids more than twice during the 1-year study
- pregnancy or breast feeding

Patient Selection Criteria for the Long-Term Adult Safety Study FG-06-12

- Male and female patients were eligible for study participation if they met the following criteria:
- at least 18 years of age
- a diagnosis of atopic dermatitis based on Hanifin and Rajka criteria
- at screening visit and Day 1, an atopic dermatitis score of at least 4.5 based on the Rajka and Langeland grading system
- a disease involvement of at least 5% but less than 60% of the total body surface area
- provided written informed consent
- had not used, or agreed to discontinue use at least four weeks before the Day 1 visit, systemic corticosteroids and other investigational drugs
- agreed not to receive ultraviolet light treatments (UVA, UVB), nonsteroidal immunosuppressants, and topical corticosteroids from Day 1 onwards
- agreed to restrict the use of systemic corticosteroids, inhaled corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) during the study
- showed a negative pregnancy test on Day 1 and agreed to practice effective birth control during the study if a female of child-bearing potential (Note: as per Amendment 1, birth control had to be continued for six weeks after study completion).
- agreed to and showed the ability to comply with study requirements and to return to the clinic for scheduled visits.

- Any of the following conditions barred the patient from entry into the study:
- serious skin disorder other than atopic dermatitis
- likely requirement for more than 1 mg/day of inhaled corticosteroid during the study
- history of more than two courses of systemic corticosteroid treatment per year
- chronic use of NSAIDs (*e.g.*, for arthritis)
- known hypersensitivity to macrolides or any excipient of the ointment
- clinically significant abnormal laboratory values determined from blood collected at the screening visit
- cancer or a history of cancer (including skin cancer), an HIV-positive status, or a chronic disease that was unstable or uncontrolled
- clinically significant impairment of renal or hepatic function
- pregnancy or breast-feeding
- previous enrolment in this study
- participation in another clinical study with an investigational drug or receipt of an investigational drug within 30 days before the screening visit (upon initiation of Amendment 1)
- on Day 1, development of a new condition after the screening visit which warranted exclusion from the study.