CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 50777

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 50-777

1 General Information

1.1 NDA submission number 000

1.2 Applicant identification

1.2.1 *Name*

Fujisawa Healthcare, Inc.

1.2.2 *Address and telephone number:*

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1.2.3 *Name of company official or contact person:*

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1.3 Submission/review dates

1.3.1 Date of submission (date of applicant's letter)
September 8, 1999

1.3.2 CDER stamp date
September 9, 1999

1.3.3 Date submission received by reviewer
September 21, 1999

1.3.4 Date review begun
November 17, 1999

1.3.5 Date review completed
June 19, 2000

1.4 Drug identification

1.4.1 Generic name
Tacrolimus (FK506) 0.03% and 0.1% Ointments

1.4.2 Proposed trade name
Protopic 0.03% and 0.1% Ointments

1.4.3 Chemical name
Macrolide: see Chemistry

1.4.4 Chemical structure:
See Chemistry

1.4.5 Molecular formula
$C_{44}H_{69}NO_{12}\cdot H_2O$

1.4.6 Molecular weight
822.05

1.5 Pharmacological Category

Immunosuppressant

1.6 Dosage Form

Ointment

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ON ORIGINAL

1.7 Route of Administration

Topical

1.8 Proposed Indication & Usage section:

Short and long term treatment of the signs and symptoms of atopic dermatitis

1.9 Proposed Dosage & Administration section:

From the proposed label:

[ ]

1.10 Related Drugs

Prograf capsules (NDA 50-708) and injection (NDA 50-709) for the prophylaxis of organ rejection in patients receiving allogeneic liver transplants. The active drug is FK506 in both forms.

Other related drugs are Cyclosporin A and Rapamycin.

Cyclosporin A (Neoral) has been approved for the oral treatment of recalcitrant psoriasis.

1.11 Material Reviewed

1.11.1 NDA volumes reviewed

NDA Volumes Reviewed and their Contents

Volume	Contents
1.1,2	Application Summary
1.41-58	Human PK and Topical Safety
1.59-130	Clinical
11/9/99	Amended tables of Summary
Su.1,2	120 Day Safety update
2/11/2000	Re. Blood levels in ped. study
4/21, 5/18/2000	Latest stat. & efficacy requests
6/2, 6/28/2000	Lymphoma Issues

1.11.2 Regulatory Documents Reviewed

Minutes of End of Phase 2 meeting, minutes of Pre-NDA meeting.

1.11.3 Non-Regulatory Documents Reviewed

Literature Searches on the FK506, clinical experience, molecular biology and its safety including incidence of lymphomas.

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1.12 Regulatory Background

1- **December 15, 1994**: Sponsor filed IND# ——

2- **October 28, 1996**: End of Phase 2 Meeting; Clinical comments including a subsequent clarification (11/1/96):

- Agency suggested assessment of both 0.03% and 0.1% ointments in both adults and children, unless the sponsor was willing to study and market the lower concentration only.
- Agency required 90% improvement in physician global as endpoint.
- Two clinical studies in one age group (e.g. adults) and one study in the other age group (e.g. pediatric). If the results of the latter study are not confirmatory to the former studies, then a second study (pediatric) will be needed.
- At least 300 patients will be exposed to the maximally proposed dosage for a minimum of 6 months to assess safety.

3- **April 6, 1999**: Pre-NDA Meeting; Clinical comments summary:

- The five pivotal studies are adequate for filing an NDA.
- If there is no significant advantage of the 0.1% over the 0.03% ointment, the latter will be the only approvable product.
- Submission of all data and full reports of foreign studies is recommended.
- Submission of all available data on the higher concentrations (0.3%, 0.5%) is recommended for their implications on safety evaluation.
- An ISS including all safety data from all available studies should be submitted.
- Additional analysis of ages 2-6 years of age is strongly recommended.
- Photographic documentation of the three pivotal efficacy studies should be submitted, digitized onto CD.
- The pivotal and the long-term safety studies should show the data by individual study sites to allow comparison of sites within each study. Also, the EASI scores for individual signs and symptoms should be available in these studies.
- Adverse event tabulations should include all causalities, i.e. irrespective of whether they are thought to be related or unrelated to the drug.
- Pediatric Rule implementation: The immunological parameters studied in the long-term adult study were not studied in the log-term pediatric study. The safety of the drug in the pediatric group has to be thoroughly assessed before making any decision regarding the adequacy of the pediatric development program.
- Full reports of the pivotal and long-term safety studies as well as the ISS and ISE should be additionally presented as MS Word 97 electronic documents.
- Include case report tabulations for phase 1 and phase 2 studies in the submission.

4- **April 30, 1999**: Sponsor submitted IND —— SN-123, a request for clarification, that was reviewed 6/23/99 and the responses were communicated back to the sponsor.
In summary, the proposed formats were acceptable, except that:

- IF phase 1 studies FG 04 AND FG 17 will not be included in ISS, although the sponsor agreed to include all Phase 1 studies in ISS in this FHI's Proposal, then an explanation is needed from the sponsor.
- The sponsor is reminded that Case report form tabulations are to be included in the clinical section.

2 Table of Contents

3 Chemistry/Manufacturing Controls

See Dr. S. Hathaway's Review (unavailable when Medical Officer Review was completed).

4 Animal Pharmacology/Toxicology

See Dr. Barbara Hill's Review.

The results of the animal carcinogenicity study and its Pharm/Tox and Statistical reviews were discussed in CAC meeting on March 14, 2000. The statistically significant increases in pleomorphic lymphomas and undifferentiated lymphomas in topically treated mice, both in the male and female groups, were the main issues of concern. The executive CAC recommendation and conclusions were discussed in a Divisional meeting on March 29, 2000. A request for further information was prepared and transmitted by fax to the sponsor on March 30, 2000. A copy of this request for further information is attached **(Attachment #1)**.

5 Human Pharmacokinetics/Pharmacodynamics

See Dr. V. Tandon's Clinical Pharmacology/Biopharmaceutics.

6 Microbiology

See Dr. N. Sweeney's review.

7 Human Clinical Experience

7.1 Foreign Experience

The drug substance, tacrolimus (FK506) was originally approved in USA on April 8, 1994 in Prograf capsules (NDA 50-708) and injection (NDA 50-709) for prophylaxis of organ rejection in patients receiving allogeneic liver transplants.

Tacrolimus ointment (Protopic [tacrolimus] ointment 0.1%) received marketing approval for the treatment of atopic dermatitis in Japan on June 16, 1999.

7.2 Post-Marketing Experience

No post-marketing adverse events have been reported in the 120-day safety update from Japan where the ointment has been recently approved.

8 Clinical Studies

8.1 Introduction

8.1.1 Atopic Dermatitis:

A summary of the clinical entity and its current standard of care, with recent references and reviews, are submitted by the sponsor in section 3.11.1 in the "Application Summary".

8.1.2 Human Studies Submitted in the NDA:

The following tables list all human studies submitted in NDA 50-777, with enrollment numbers for study drug and active control.

Table 1: Summary of the 28 Clinical Studies Presented in the Submission
(Pivotal/Core studies bolded)

Protocol Number	Study Design	Patient Population [actual age]	Regimen	No. Treated‡‡
A- Eleven Clinical Pharmacology/Pharmacokinetic Studies				
1- Six Patch Test Studies in Healthy Volunteers				
94-0-004† Phase 1-Patch Test	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	Open-label, intrasubject, phototoxicity 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	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	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	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	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
2- Three Pharmacokinetic (PK) Studies				
FG-06-04‡ Phase 1-PK	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-PK	Open-label pharmaco-kinetic study	Adult and pediatric AD patients [aged 5-75 years]	0.3% tacrolimus ointment once daily Day 1 and 8, twice daily Days 2-7, 50 to 5000 cm^2 area	39
FJ-106§ Phase 2-PK	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%)
3- Two Mechanism of Action (Pharmacology, PD) Studies				
FG-06-17‡ Phase 2*-PD	Double-blind, randomized, single-center, clinical pharmacology (collagen synthesis) study	Healthy subjects and AD 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 (Veh)]
97-0-030† Phase 2-PD	Double-blind, randomized, active control immuno-histological study (biopsy study)	Adult AD 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 (0.1% tacrolimus) 11 (TA)
B- Seventeen Clinical Studies				
1- Controlled Studies: Three Phase 3 Pivotal Studies ("Core Studies")				

97-0-037† Phase 3	**Double-blind, randomized study in patients with moderate or severe atopic dermatitis**	**Children [aged 2-15 years]**	**0.03% or 0.1% tacrolimus ointment or vehicle twice daily for 12 weeks**	**351 117 (0.03%) 118 (0.1%) 116 (Veh)**
97-0-035†# Phase 3		**Adults [aged 15-77 years]**		**304 103 (0.03%) 99 (0.1%) 102 (Veh)**
97-0-036† Phase 3		**Adults [aged 16-79 years]**		**328 108 (0.03%) 110 (0.1%) 110 (Veh)**
2- Controlled Studies: Ten Studies Supportive of Safety				
95-0-003† Phase 2	Double-blind, randomized, dose response study	Children with moderate or severe AD [aged 6-16 years]	0.03%, 0.1%, or 0.3% tacrolimus 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	Double-blind, randomized, parallel group, dose response study	Patients with AD [aged 13-63 years]	0.03%, 0.1%, or 0.3% tacrolimus 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	Double-blind, randomized, sequential group, dose-escalation study	Children with moderate or severe AD [aged 3-6 years]	0.03% or 0.1% tacrolimus ointment or vehicle twice daily for up to 3 weeks	33 12 (0.03%) 13 (0.1%) 8 (Veh)
95-0-013† Phase 2	Double-blind, randomized, sequential group, dose-escalation study	Adults with moderate or severe AD [aged 17-69 years]	0.03%, 0.1%, or 0.3% tacrolimus ointment or vehicle twice daily for up to 3 weeks	26 7 (0.03%) 6 (0.1%) 7 (0.3%) 6 (Veh)
FJ-103§ Phase 2	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	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	Double-blind, randomized, parallel group study	Adult patients with chronic-type AD [age 16-56 years]	0.1%, 0.3%, or 0.5% tacrolimus ointment or 0.12% betamethasone valerate 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	Double-blind, randomized, parallel group study	Adult patients with chronic-type AD on the trunk/ extremities [age 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	Randomized parallel group comparative study	Adult AD patients with disease affecting the trunk/extremities [age 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	Randomized parallel group comparative study	Adult AD patients with disease affecting the face/neck [age 16-70 years]	0.1% tacrolimus ointment or 0.1% alclometasone dipropionate (AL) twice daily for 1 week	151 75 (0.1%) 76 (AL)
3- Four Uncontrolled Studies				
a- Two Long-Term Safety Studies ("Core Studies")				
96-0-025† Phase 3	**Open-label, single concentration, long-term, multicenter study**	**Children with moderate or severe AD [aged 2-15 years]**	**0.1% tacrolimus ointment twice daily for up to 1 year**	**255**
FG-06-12‡ Phase 3	**Open-label, single concentration, long-term, multicenter study**	**Adults with moderate or severe AD [aged 18-70 years]**	**0.1% tacrolimus ointment twice daily for up to 1 year**	**318 [316 with post-baseline data]**
b- Two Additional Studies with Supportive Safety Data				
FJ-111§ Phase 3	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	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. BV: 0.12% betamethasone valerate. AL: alclometasone dipropionate. Veh: vehicle. TA: triamcinolone acetonide. † United States ‡ Europe. § Japan; number of treated patients was determined based on Japanese case report forms. $ Ongoing study, 1 year data available.

‡‡ 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. Adverse events for these patients are listed in Section 8.4.13 (ISS Statistical Appendix 8.4.13.10.5); see also Section 8.7 of this submission for treatment group.

* Included as a Phase 1 study in global experience analysis in view of its *patch-test like* study design.
# 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.
§§ Study FJ-110 is an extension study of Study FJ-109; patients were enrolled in the 0.1% tacrolimus ointment treatment group Study FJ-109.

8.2 Dermal Toxicity Studies

8.2.1 Cumulative Irritation, Protocol 94-0-007

Method: Thirty subjects were recruited from males and females in the [redacted] area. These subjects were between 18-65 years of age. Each subject was examined to assure that he was free of atopic dermatitis/eczema, psoriasis, asthma or other skin condition which may interfere with the evaluation of the study results. Also, they were questioned to assure they were not taking any antihistamines, corticosteroids, analgesics or anti-inflammatory drugs. Females were ineligible if they were pregnant or nursing. Females were required to be post-menopausal, surgically sterile or using active form of birth control.

Each subject was patched with a total of 8 patches on the subject's back. Patch sites were marked with skin marker pen. Samples (0.12 g) of each test product were applied on the absorbent area (3 sq. cm) of each occlusive patch [redacted] These were applied daily to the back of volunteers, except on Sundays, for 21 consecutive days according to a predetermined randomization code. The patches were secured with tape and marked to identify the code for each test material, so that subsequent patches containing the same test material can be applied to the same location.

The patches were removed 24 hours later (except Saturday patches: 48 hours) and scored within 5 minutes of removal. The scoring followed a 5-point scale: 0 = no sign of irritation, 1 = slight erythema, 2 = noticeable erythema with slight infiltration, 3 = erythema with marked edema, and 4 = erythema with edema and blistering. Applications were discontinued for any subject with a score of 4, and the score of 4X was recorded for the remaining days of the study.

The irritation index for each product was calculated by dividing the sum of grades for all subjects for all days by the maximum possible score of 2160 (=30 subjects X 18 grades X 4).

Results: Three subjects were dropped from the study because of the use of prohibited medications. The following irritation index values were obtained with 18 applications to the back of each of 27 volunteers, under occlusion, over a 3-week period:

1- Tacrolimus ointment, 0.03%	58/2160
2- Tacrolimus ointment, 0.1%	31/2160
3- Tacrolimus ointment, 0.3%	35/2160
4- Ointment vehicle	38/2160
5- Calcipotriene ointment 0.005%	745/2160
6- Hydrocortisone ointment 1%	51/2160

7- Betamethasone valerate 0.1%	53/2160
8- Sodium lauryl sulfate 0.5%	1634/2160

Reviewer's Comment: There is slight to moderate irritation with the three concentrations of Tacrolimus ointment tested as well as with the vehicle. The 0.03% ointment appears to have more potential for irritation than the vehicle or the higher concentrations. It is to be noticed that most of this irritation was observed in the earlier applications (days 10-15, total scores range from 4 to 6), and the irritation disappeared or improved with repeated applications (days 19-21, total scores = 2). The other steroid ointments tested were generally equally irritating. Calcipotriente ointment 0.005% was clearly a much stronger irritant in comparison to all other ointments tested.

The degree of irritation observed with the Tacrolimus ointments appears to be acceptable.

8.2.2 Repeated Insult Patch tests:

8.2.2.1: Protocol 94-0-004

This was an open-label study of 7 test products on 30 normal subjects. The investigator's clinical impression was that Tacrolimus ointment 0.03%, 0.1% and 0.3%, its vehicle, hydrocortisone ointment 1% and betamethasone valerate 0.1% were slightly irritating and were not sensitizers, whereas Calcipotriene ointment 0.005% was quite irritating but probably not a sensitizer.

Reviewer's Comment: Because of the small number of subjects and the open-label design, this study is of little regulatory significance. The sponsor was informed of the need for a larger double-blind study. This was the reason for carrying out the second protocol (95-0-011).

8.2.2.2: Protocol 95-0-011

Subjects (n = 229) were recruited as previously described in Protocol 94-0-007. This was a double-blind study conducted at a single investigative site to determine the contact sensitization potential of Tacrolimus ointment (0.03, 0.1 and 0.3%) and ointment vehicle. All 4 products were applied, under occlusive patches, to the backs of 229 adult volunteers. The patches were removed after 48 hours, the sites were then graded for irritation using a 5-point scale (as described with Protocol 94-0-007). This sequence of applying medications, patching and grading was repeated a total of 9 times over a 3 week period. After a 2-week rest period, one challenge application was made. Patches were applied to sites not previously exposed to the test article, and left in place for 48 hours. The sites were then graded for irritation at 5 minutes, 24 hours and 48 hours after removal of the patches to assess sensitization potential.

Of the 229 subjects enrolled, 198 completed the study. Six subjects were dropped because of serious adverse events unrelated to the products applied, four were dropped because they took prohibited medications, and 18 for noncompliance due to missed visits.

The "Investigator's clinical impression" of each of the four products tested, Tacrolimus ointments 0.03%, 0.1% and 0.3% and its vehicle, was "Product is moderately irritating and not a sensitizer".

Reviewer's Comment: The sponsor submitted line listing of the evaluation results for each of the test products in Vol. 51 (attachment), section 6.5.1.5, p 27-46. There were no summary tables or SAS data submitted for this protocol report.

Induction Phase: On examination of these line listings it was noticed that the irritation scores during the induction phase were generally higher than those reported in the cumulative irritation study (protocol 94-0-007). For example, in the present protocol, the 0.03% ointment showed a score of 2 (erythema with slight infiltration) in 32 subjects (16%) on one of the 9 evaluations, in 12 subjects on two evaluations, in 8 subjects on three evaluations, in 7 subjects on four evaluations, in 4 subjects on 5 evaluations, and in 2 subjects on 6 of the 9 evaluations. One subject had a score of 3 (erythema with marked edema) on two of the 9 evaluations. In protocol 94-0-007, only two subjects (7%) showed a score of 2 at any evaluation (one subject on two, and another on four of the 18 evaluations). This difference does not appear to be significant especially if it is noticed that in the present protocol the applications were kept under occlusion 48 hours, whereas in protocol 94-0-007 occlusion was only for 24 hours. Also, a similar degree of irritation was noticed with the vehicle.

Challenge Phase: 1) A score of two (erythema with slight infiltration) was observed only once. This was in subject #152 with 0.1% Tacrolimus ointment. However, this was observed only in the first evaluation (few minutes after patch removal) and dropped to score of 0 on the second and third observations (24 hr and 48 hr after patch removal). Therefore, this is mostly an irritation reaction rather than a contact sensitization reaction. 2) A score of 1 (slight erythema) was observed more frequently. Its observation in the second or third evaluation may indicate a mild contact sensitization reaction. This becomes very likely if the subject did not show any erythema in the first evaluation (few minutes after patch removal). This latter situation occurred with subjects # 1, 35, 73, 115 (total = 4) with 0.03% Tacrolimus ointment, with subjects # 27, 51, 81, 109, 115, 142, 168, 214, 229 (total = 9) with 0.1% Tacrolimus ointment; with subjects # 26, 115, 136, 144, 228, 229 (total = 6) with 0.3% Tacrolimus ointment, and with subjects # 19, 44, 84, 115, 131, 135, 136, 142, 155, 214, 219 (total = 11) with the ointment vehicle. Subject # 115 showed this pattern of reaction with all of the four test products. This is very likely to be a true positive reflecting a mild contact sensitization reaction to one or more of the ingredients of the ointment vehicle. Re-challenge was not done with the products or their individual ingredients to confirm this reaction and identify the sensitizing ingredient.

The present reviewer believes that this product has produced a mild contact sensitization reaction in 0.5% of the subjects tested, and that the vehicle is the sensitizing agent.

8.2.3 Phototoxicity study, Protocol 94-0-005 :

Subjects (n = 12) were recruited as previously described in Protocol 94-0-007, except that the prohibited medications included tetracyclines and thiazides. Each subject received a total of 14 applications on the subject's back, two of each test product. Within 7 days prior to the start of the study, each subject's MED was determined and recorded. On the first day test sites were identified by letters A-G in each set. One set received product and UV light; the second set received product but no light. An additional single site received only UV light. Each site was tape-stripped to the glistening layer.

Test products (0.12 g of each) were applied directly to the skin (3 sq. cm area sites). One set of the treated sites was covered so that it could not be irradiated. The second set, as well as the additional product-free site were irradiated with UVA (10.5 times MED equivalent) and UVB (0.5 MED) using a 1000 watt ——— Simulator provided with a removable UVB filter. Evaluations of skin irritation were made using 5-point scale (as described in Protocol 94-0-007) at 5 minutes, 3 hours, 24 hours and 48 hours after the last irradiation.

The "Investigator's clinical impression" of each of following test products was reported:

1- Tacrolimus ointment, 0.03%	This product is not phototoxic
2- Tacrolimus ointment, 0.1%	This product is not phototoxic
3- Tacrolimus ointment, 0.3%	This product is not phototoxic
4- Ointment vehicle	This product is not phototoxic
5- Calcipotriene ointment 0.005%	This product is not phototoxic
6- Hydrocortisone ointment 1%	This product is not phototoxic
7- Betamethasone valerate 0.1%	This product is not phototoxic
8- Sodium lauryl sulfate 0.5%	This product is not phototoxic

Reviewer's Comment: These conclusions appear to be justified.

8.2.4 Photocontact Allergy tests:

8.2.4.1: Protocol 94-0-006

This was an open-label study of 7 test products on 30 normal subjects. The investigator's clinical impression was that Tacrolimus ointment 0.03%, 0.1% and 0.3%, its vehicle, hydrocortisone ointment 1%, betamethasone valerate 0.1%, and Calcipotriene ointment 0.005% did not cause photoallergy.

Reviewer's Comment: Because of the small number of subjects and the open-label design, this study is of little regulatory significance. The sponsor was informed of the need for a larger double-blind study. This was the reason for carrying out the second protocol (97-0-026).

8.2.4.2: Protocol 97-0-026

This was a double-blind study enrolling 228 subjects. The subjects were recruited as previously described for Protocol 95-0-11. The study was conducted at one investigative site to determine

the photosensitizing potential of Tacrolimus ointments (0.03% and 0.1%) and ointment vehicle. These 3 products were applied in duplicate, under occlusive patches to the backs of adult volunteers. The patches were removed after 24 hours. One set of sites was covered, and the other set as well as an additional control (no test product applied) site were exposed to UVA/UVB light (2 MED, from 1000 watt [redacted] Simulator). Immediately after light exposure (5 minutes) and 24 (or 96) hours after exposure, all sites were graded for irritation using 5-point scale (as described previously in Protocol 94-0-007). The sequence of patching, irradiation and evaluation was repeated 6 times over a 3-week induction period. After a one-week rest period, one challenge application of all test materials was made at duplicate sites, followed (next day) by irradiation with UVA light (10 MED equivalents). Evaluations were made 5 minutes, 24 hours and 48 hours after irradiation to assess photosensitization potential.

Of the 228 subjects enrolled, 216 completed the study. Five subjects were dropped because of serious adverse events unrelated to the products applied, three because of missed visits, three at the subjects' request, and one for family emergency.

The "Investigator's clinical impression" of each of the three products tested, Tacrolimus ointments 0.03%, 0.1% and its vehicle, was "Product does not cause photosensitization". The tabulated results showed that during challenge phase, the vehicle showed score of 1 in 8.4% of the observations in the irradiated areas and in 3.7% in the non-irradiated areas. All other scores were zeros. The corresponding values for the 0.03% Tacrolimus ointment were 17.7% and 11.4%, and for the 0.1% ointment, 16.3% and 9.8%, respectively.

Reviewer's Comment: The finding of 1) no scores above one in the challenge period, 2) no score above 0 on the third observation after challenge, and 3) very few scores of 1 in the second observation after challenge, makes the sponsor's conclusion justifiable. The small differences between the vehicle and ointment in the incidence of scores of 1 may be attributed to the slightly higher irritation produced by the Tacrolymus ointment, especially that almost all of these 1 scores were observed only in the first observation point, 5 minutes after tape removal and irradiation. The small differences between the irradiated and non-irradiated sites in the incidence of scores of 1 may be attributed to the slightly higher irritation produced by the irradiation (10 times MED equivalent of UVA light).

8.3 Review of efficacy:

Indication #1

Treatment of atopic dermatitis in adults

8.3.1 Trials #1&2: 97-0-035 & -036

8.3.1.1 Objective/Rationale

These two studies were designed to determine the safety and demonstrate the efficacy of topically applied tacrolimus ointment (0.03% or 0.1%) in treating the signs and symptoms of moderate to severe atopic dermatitis involving at least 10% of the body surface area in adult patients.

8.3.1.2 Design

These two pivotal studies were similarly designed with respect to objective, procedures, treatment duration, endpoints and analyses. Both studies were randomized, double-blind, parallel group, three-arm, vehicle-controlled, multicenter studies. There were 21 centers (23 investigators) in study 97-0-35 and 20 centers (20 investigators) in study 97-0-36. Patients applied a thin coat of tacrolimus ointment (0.03% or 0.1%) or vehicle twice daily (q10-14 hours) to areas of active disease as defined by the investigator at the baseline visit. The maximum duration of treatment was 12 weeks. In patients with clearing of atopic dermatitis, treatment was to have continued for 1 week after clearing. There was a 2-week follow-up visit after treatment discontinuation.

Patients were evaluated at baseline; during treatment (Weeks 1, 2, 3, 6, 9); at Week 12 or end of treatment, if earlier; and at the end of the study (2 weeks posttreatment/Week 14). Adverse events were recorded through 2 weeks posttreatment. The primary efficacy endpoint was the incidence of success obtained from the Physician's Global at the end of treatment. Success was defined as a rating of cleared or excellent improvement (90-100% improvement in areas defined for treatment at baseline). Secondary endpoints included EASI score, percent of body surface area affected, Physician's Assessment of Individual Signs of Atopic Dermatitis, and Patient's Assessment of Pruritus.

The primary patient population for efficacy analyses as prospectively defined in the analysis plan for each study was the evaluable patient subset comprised of all randomized patients who received study drug for at least 3 consecutive days (minimum of five applications) beginning at baseline and had at least one "on treatment" value for the Physician's Global. However, at the pre-NDA meeting in April 1999, the FDA requested the primary patient population for efficacy analyses be the intent-to-treat population (ITT), all randomized patients who were dispensed the treatment medication. For the pivotal studies, this ITT population is identical to the modified intent-to-treat population (MITT) presented in the individual study reports (all randomized patients who received at least one dose of study drug), since the only randomized patient who did not receive at least one dose of study drug (in the vehicle arm of study 97-0-035) was not dispensed study drug (i.e., ITT = MITT).

In each individual study, Fisher's exact test was performed to determine if there was a statistically significant difference in the success rate among the three treatment groups. Since statistical significance at the 5% level was obtained in both studies, Fisher's exact test was used for the pairwise comparison of the three treatment groups, each at the 5% level of significance.

8.3.1.3 Protocol Overview

8.3.1.3.1 Population, procedures

The patient's eligibility for the study was determined based on an informational interview, an examination to confirm the diagnosis of atopic dermatitis and its severity, and the results of a urine pregnancy test (if female). Written informed consent was obtained prior to enrollment in the study.

Inclusion Criteria

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 [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatov 1980;Suppl 92:44-7.] (for details see: Appendix 14.1.1, protocol).

- moderate to severe atopic dermatitis based on the Rajka and Langeland grading system [Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol (Stockh) 1989;Suppl 144:13-4.] involving at least 10% of the body surface area (for details see: Appendix 14.1.1, protocol). This grading system is based on the total scores on three aspects: extent, course and intensity (as measured by pruritus).
- at least 16 years of age
- 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 (see Appendix 14.1.1, protocol, for a detailed description and specific washout time frames which ranged from 7 days to 6 weeks for systemic medicines or medicated topical treatments).
- 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

Exclusion Criteria

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

Overview of Schedule of Procedures

The schedule of study procedures, including an evaluation flow chart, can be found in Appendix 14.1.1, protocol. Patients were evaluated at baseline/Day 1; during treatment (Weeks 1, 2, 3, 6, 9); Week 12 or end of treatment, if earlier; and at the end of the study (2 weeks posttreatment/Week 14). Additional evaluation visits were conducted if necessary. Adverse events were recorded from Day 1 through 2 weeks posttreatment. Blood was collected by venipuncture from patients on baseline/Day 1, Week 1, Week 3 and Week 12/end of treatment in order to determine laboratory profiles.

To aid in data collection, patients were asked to record drug application information, deviations from instructions, the use of concomitant medications and any symptoms, complaints, illnesses or accidents in a diary throughout the study. These entries were reviewed at scheduled visits and relevant information transferred to the case report form. At four centers, photographs were taken during the study to document disease status.

The efficacy and safety variables in this study are those commonly used in studies of this type and are briefly described in the following subsections; refer to Appendix 14.1.1, protocol, for a detailed presentation of assessments and grading systems.

Reviewer's Comment:

The exclusion of patients with clinically infected atopic dermatitis from the protocol leads to significant implications and should be addressed in labeling.

8.3.1.3.2 Endpoints defined

Efficacy

Optimally, all the physician-based efficacy assessments should have been performed by the same physician rater. However, a secondary ("backup") rater may have performed assessments in the event of an emergency or unavailability of the physician for any of the postbaseline visits. This secondary rater was required to have been present at the baseline evaluation and to have agreed with the primary rater on the baseline ratings.

At each visit, patient assessments were made prior to the physician assessments in order to avoid bias.

Primary Efficacy Endpoint

The primary efficacy endpoint was the incidence of success obtained from the Physician's Global at the end of treatment. For the Physician's Global, changes in the overall status of the atopic dermatitis lesions identified for treatment at baseline were rated using the following scale:

Physician's Global Scale

	Percent Improvement†
Cleared	100
Excellent Improvement	90 – 99
Marked Improvement	75 – 89
Moderate Improvement	50 – 74
Slight Improvement	30 – 49
No Appreciable Improvement	0 – 29
Worse	<0

† Except for residual discoloration

Success was defined as a rating of cleared or excellent improvement (i.e., ≥90% improvement in the areas defined for treatment at baseline).

Secondary Efficacy Endpoints

Secondary efficacy endpoints included the change from baseline to the end of treatment for the Eczema Area and Severity Index (EASI), percentage of body surface area affected (% BSA), the Physician's Assessment of Individual Signs of Atopic Dermatitis, the Patient's Assessment of Treatment Effects (Overall Response and Pruritus), and the incidence of recurrence. In addition, the Area under the Curve (AUC) for the Physician's Global and the Patient's Assessment of Overall Response scores over time, standardized by dividing by the total number of treatment days, were calculated by the trapezoidal rule.

Eczema Area and Severity Index (EASI)

The Eczema Area and Severity Index score was developed by Dr. [redacted] in order to provide an overall measure of the severity of the disease. At each visit, EASI was calculated by the Sponsor based on the Physician's Assessment of Affected Body Surface Area and the Physician's Assessment of Individual Signs of Atopic Dermatitis in each of the defined body regions.

Physician's Assessment of Affected Body Surface Area

The percentage of body surface area affected by atopic dermatitis (0%-100%) was estimated by the investigator for each body region (head and neck, trunk, upper limbs, and lower limbs) at each visit. This assessment was made for the baseline treatment areas and for affected areas not included in the baseline treatment areas.

Physician's Assessment of Individual Signs of Atopic Dermatitis

The investigator rated six clinical signs of atopic dermatitis (erythema, edema/induration/papulation, excoriation, oozing/weeping/crusting, scaling, lichenification) in each body region (head and neck, trunk, upper limbs, and lower limbs).
A standard severity grading scale (0=absent, 1=mild, 2=moderate, 3=severe) was used to rate each sign/symptom. Intermediate ratings (i.e., 0.5, 1.5, 2.5) were not permitted.

The calculation of the EASI score is described in detail in Appendix 14.1.1 (protocol, Appendix IV). Briefly, for each of the body regions, the grades for four of the six clinical signs of atopic dermatitis were totaled (erythema grade + edema/induration/papulation grade + excoriation grade + lichenification grade = total grade) and this total grade (TG) multiplied by a converted affected area score (AS).

The AS was determined by taking the physician's assessment of the percentage of body surface area affected by atopic dermatitis in each region, and converting it to a score based on a 7-point scale as follows: 0=0%, 1=1-9%, 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89%, and 6=90-100% affected area.

Only four of the six clinical signs of atopic dermatitis are part of the EASI score developed by Dr. [redacted] Oozing/weeping/crusting, and scaling were evaluated since these signs/symptoms are of clinical interest, but they are not included in the EASI calculation.

The Total EASI score was calculated based on the following equation:

$$\text{SCORE} = (\textit{[head/neck TG X AS]} \times 0.1) + (\textit{[upper limbs TG X AS]} \times 0.2) + (\textit{[trunk TG X AS]} \times 0.3) + (\textit{[lower limbs TG X AS]} \times 0.4)$$

The highest possible EASI score is 72 (i.e., TG = 12 and AS = 6 for each of the body regions).

[Note: In order to facilitate future comparisons with results obtained in European studies, a modified EASI score, which is a combination of the [redacted] EASI score and a "Patient Assessment of Pruritus" score, converted from an analog scale to a 4-point scale (0-3) and then multiplied by AS (0-6) to a maximum score of 18, was also calculated. Thus the highest possible modified EASI score is 90 (72 + 18). Details of this calculation can be found in Appendix 14.2.1, Statistical Methods.]

Patient's Assessment of Overall Response

At each visit, the patients provided their perception of the change from baseline in overall (global) disease (e.g., how the atopic dermatitis looked, how it felt, how others reacted to it). Change from baseline was assessed as: "Much Better", "Better", "Slightly Better", the "Same", "Slightly Worse", "Worse", or "Much Worse". Patient's assessments were made prior to the physician's assessments.

Patient's Assessment of Pruritus

The amount and intensity of pruritus experienced during the previous 24-hour period was assessed using a 10 cm visual analog scale where 0 cm = "No Itch" and 10 cm = "Worst Itch Imaginable."

Recurrence

Recurrence was defined as the reappearance or worsening of atopic dermatitis in the baseline defined treatment areas which warranted therapy with the investigative agent. All patients considered by the investigator to be treatment successes at the end of treatment who subsequently experienced a recurrence during the posttreatment period were to be assessed with respect to EASI score, percent affected body surface area, Physician's Assessment of Individual Signs of Atopic Dermatitis, and Patient's Assessment of Pruritus. The investigator also documented the date of recurrence.

Additional Efficacy Assessments

Additional efficacy assessments included the distribution of responses in the Physician's Global (described above, in section on "Primary Efficacy Endpoint") at end of treatment and through Week 3, and the time to first improvement in Physician's Global (at least excellent improvement, at least marked improvement, at least moderate improvement, at least slight improvement; for details see Appendix 14.2.1).

Safety

Safety was assessed based on the incidence of adverse events and changes from baseline in clinical laboratory profile. An adverse event (AE) was defined as any undesirable experience occurring to a patient during the clinical trial whether or not considered related to the study medication. Such occurrences could have been new (emerging during the study) or have represented a worsening of an existing medical condition. All adverse events through 2 weeks posttreatment, whether ascertained through patient interview, physical examination, laboratory findings, or other means, were recorded. In order to better assess the adverse event experience in

this study, adverse events were categorized as application site events and nonapplication site events at the time of data collection.

A serious adverse event was defined as any experience that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, or was considered an important medical event. All serious adverse events were to be immediately reported by telephone or facsimile, followed within 72 hours by a written description of the circumstances surrounding the event, to the Fujisawa Healthcare, Inc. monitor or designee.

Laboratory parameters determined included:

- Hematology - hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, eosinophil count (manual count), and platelet count
- Chemistry - sodium, potassium, chloride, blood urea nitrogen, serum creatinine, direct and total bilirubin, transaminases (SGOT/AST; SGPT/ALT), alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transpeptidase, glucose, uric acid, magnesium, IgE
- Urine pregnancy test for female patients (baseline and end of treatment only)

Other: Quality of Life Measurement

The Dermatology Life Quality Index (DLQI) was used to assess the physical and psycho-social aspects of the disease state [Finlay AY, Khan GK, Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Clinical and Experimental Derm 1994;19:210-16.]. Patients completed the questionnaire before the physician's assessments (in order to avoid bias) at baseline, Week 3 and Week 12/End-of-Treatment. DLQI scores were evaluated by [redacted], a commercial group [redacted]; the results are presented in a separate report.

8.3.1.4 Study Results

8.3.1.4.1 Demographics

The patient disposition and population subsets are summarized in Table 2 and Table 3.

Table 2: Patient Disposition [1]

Variable		Treatment Group			Total
		Vehicle	Concentration of Tacrolimus Ointment		
			0.03%	0.1%	
Randomized :	in #035 [2]	103	103	99	305
	#036	110	108	110	328
Intent-to-Treat:	#035	102	103	99	304
	#036	110	108	110	328
Completed Treatment					
	#035	*38 (37.3%)*	*73 (70.9%)*	*71 (71.7%)*	*182 (59.9%)*
	#036	*29 (26.4%)*	*77 (71.3%)*	*86 (78.2%)*	*192 (58.5%)*
Discontinued	#035	*64 (62.7%)*	*30 (29.1)*	*28 (28.3%)*	*122 (40.1%)*
	#036	*81 (73.6%)*	*31 (28.7%)*	*24 (21.8%)*	*136 (41.5%)*
Lack of Efficacy	#035	*41*	*11*	*10*	*62 (20.4%)*
	#036	*54*	*15*	*8*	*77 (23.5%)*
Adverse Event	#035	*12*	*5*	*7*	*24 (7.9%)*
	#036	*14*	*8*	*4*	*26 (7.9%)*
Administrative	#035	*11*	*14*	*11*	*36 (11.8%)*
	#036	*13*	*8*	*12*	*33 (10.1%)*

(1) Source: Tables 1 and 2 of the results section of the study reports, calculated by M.O.
(2) Studies 97-0-035 (#035), and 97-0-036 (#036).

Of note, 45% (95/212) of vehicle-treated patients discontinued the study due to lack of efficacy compared with 12% (26/211) of 0.03% tacrolimus ointment-treated patients and 9% (18/209) of 0.1% tacrolimus ointment-treated patients.

Table 3: Patient Populations

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Patients Randomized †	213	211	209	633
Patients in Intent-to-Treat Population †	212	211	209	632
Patients in Efficacy Evaluable Population ‡	179	194	189	562
Patients in Per Protocol Population ‡	133	173	164	470

Intent-to-treat population (ITT): all randomized patients who were dispensed study drug.
Efficacy evaluable population: all randomized patients who received study drug for at least 3 consecutive days (minimum five applications) beginning on Day 1 and had at least one "on treatment" value for the Physician's Global. Per protocol population: all randomized patients who completed the study without a major protocol deviation as determined during a blinded patient classification review.
† Patient No. 84515 was enrolled/randomized in adult Study 97-0-035 despite being 15 years of age. For all analyses in the ISE except for age-based analyses, this patient is considered an adult patient.
‡ Patient No. 84515 (see previous footnote) was not included in the efficacy evaluable or per protocol population.
Studies: 97-0-035 (Adult), and 97-0-036 (Adult).
Source: ISE, Table 4.

Reviewer's Comments:

Patient demographics and other baseline characteristics of the MITT (=ITT) population in studies #035 and #036 are presented in Appendices 14.3.2.1, 14.3.2.2, and 14.3.2.3. Listings by patient number are found in Appendices 14.4.1.2, 14.4.1.3, and 14.4.1.4 of the respective study reports. The data in these tables are summarized below.

No statistically significant differences among treatment groups were observed for any demographic or baseline characteristics for the ITT populations except for the duration of current AD episode in study #036. The duration (mean ± SD) was 135.4 ± 191.3 months for the vehicle treatment group compared with 100.3 ± 154.5 and 80.6 ± 142.9 months for the 0.03% and 0.1% tacrolimus treatment groups, respectively (p=0.044).

The treatment groups and patient populations were balanced with respect to age, race, and gender. For each of the two studies' ITT population, the mean age was 39 years, the majority of patients were white; however, blacks were well represented, comprising a little more than a quarter of the patients, and approximately half of tl patients' total body surface area was affected at baseline, with more than 80%of patients being affected in the head/neck region. The majority of patients had severe atopic dermatitis in both studies.

The baseline characteristics for the combined ITT populations of both studies are presented in ISE Statistical Appendix 8.3.6.2.2. No statistically significant differences among treatment groups were observed with respect to gender (43.5% males), race (66.9% Caucasian and 26.4% Black), age (4.9% above 65, 9.2% 55-64, 19.6% 45-54, median age 37), percent BSA affected (mean = 45.1%), and severity of disease (56.2% severe) at the start of the study.

8.3.1.4.2 Efficacy

8.3.1.4.2.1 Primary Efficacy Results

A- Success in the General Population:

Results for success at the end of treatment are summarized for the two adult studies combined and for each adult study separately in Table 4.

Table 4: Success Rate at the End of Treatment in Studies # 035 and 036

Study	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Intent-to-Treat Population			
Combined Studies	14/212 (6.6%)	58/211 (27.5%)	77/209 (36.8%)
97-0-035	8/102 (7.8%)	30/103 (29.1%)	35/99 (35.4%)
97-0-036	6/110 (5.5%)	28/108 (25.9%)	42/110 (38.2%)
Efficacy Evaluable Population			
Combined Studies	14/179 (7.8%)	55/194 (28.4%)	77/189 (40.7%)
97-0-035	8/89 (9.0%)	28/96 (29.2%)	35/89 (39.3%)
97-0-036	6/90 (6.7%)	27/98 (27.6%)	42/100 (42.0%)
Per Protocol Population			
Combined Studies	14/133 (10.5%)	52/173 (30.1%)	70/164 (42.7%)
97-0-035	8/66 (12.1%)	26/83 (31.3%)	31/76 (40.8%)
97-0-036	6/67 (9.0%)	26/90 (28.9%)	39/88 (44.3%)

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

Results for P values of differences in success at the end of treatment are summarized for the two adult studies combined and for each adult study separately in Table 5.

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Table 5: Test of Significance for Success Rate in Studies # 035 and 036

	P-Value†			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
Intent-to-Treat Population				
Combined Studies	<0.001	<0.001	<0.001	0.041
97-0-035	<0.001	<0.001	<0.001	0.369
97-0-036	<0.001	<0.001	<0.001	0.060
Efficacy Evaluable Population				
Combined Studies	<0.001	<0.001	<0.001	0.011
97-0-035	<0.001	0.001	<0.001	0.164
97-0-036	<0.001	<0.001	<0.001	0.037
Per Protocol Population				
Combined Studies	<0.001	<0.001	<0.001	0.016
97-0-035	<0.001	0.006	<0.001	0.248
97-0-036	<0.001	0.002	<0.001	0.043

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

Reviewer's Comments:

For all three populations (MITT, efficacy evaluable, and per protocol population), a statistically significant difference in success was observed among the three treatment groups in each study and in both studies combined. A significantly greater success rate was observed for each tacrolimus ointment treatment group compared with the vehicle in each study and in both studies combined.

In addition, the combined two adult studies (probably as a result of increase in power obtained from pooling), as well as the results of one adult study (#036, only in efficacy evaluable and per protocol populations) showed a statistically significantly greater success rate for the 0.1% tacrolimus ointment treatment group compared with the 0.03% tacrolimus ointment treatment group.

These results support efficacy of both concentrations in the adult population, and a generally higher efficacy of the higher potency.

B- Success by Population Subsets:

Success rates for **the ITT patient population** in the combined adult studies are presented by age, gender, race, baseline disease severity, and percent body surface area affected at baseline in ISE Statistical Appendices 8.3.6.4.2, and are summarized in the following tables:

Table 6: Success Rate in the Combined Adult Studies By Age

Age (Years)	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
16-64	14/202 (6.9%)	55/201 (27.4%)	74/197 (37.6%)
≥ 65	0/10 (0.0%)	2/9 (22.2%)	3/12 (25.0%)

Table 7: Test of Significance for Success Rate in the Combined Adult Studies: Age

Age (Years)	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
16-64	<0.001	<0.001	<0.001	0.036
≥ 65	0.266	0.134	0.134	0.911

Table 8: Success Rate in the Combined Adult Studies By Gender

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Males	4/95 (4.2%)	27/95 (28.4%)	27/85 (31.8%)
Females	10/117 (8.5%)	31/116 (26.7%)	50/124 (40.3%)

Table 9: Test of Significance for Success Rate in Combined Adult Studies: Gender

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Males	<0.001	<0.001	<0.001	0.638
Females	<0.001	<0.001	<0.001	0.029

Table 10: Success Rate in the Combined Adult Studies By Race (White, Black, Oriental)

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
White	10/140 (7.1%)	47/144 (32.6%)	55/139 (39.6%)
Black	4/57 (7.0%)	9/55 (16.4%)	16/55 (29.1%)
Oriental	0/10 (0.0%)	2/9 (22.2%)	5/12 (41.7%)

Table 11: Test of Significance for Success Rate in the Combined Adult Studies: Race

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
White	<0.001	<0.001	<0.001	0.227
Black	0.007	0.112	0.002	0.107
Oriental	0.078	0.138	0.027	0.390

Table 12: Success Rate in the Combined Adult Studies By Baseline Disease Severity

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Moderate	8/98 (8.2%)	35/93 (37.6%)	34/86 (39.5%)
Severe	6/114 (5.3%)	23/118 (19.5%)	43/123 (35.0%)

Table 13: Test of Significance for Success Rate in the Combined Adult Studies: Baseline Disease Severity

	P-Value from Cochran-Mantel-Haenszel Statistics			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Moderate	<0.001	<0.001	<0.001	0.911
Severe	<0.001	0.001	<0.001	0.009

Table 14: Success Rate in the Combined Adult Studies By Percent BSA Affected at Baseline

	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
10-≤25%	6/62 (9.7%)	30/66 (45.5%)	31/65 (47.7%)
>25-≤50%	6/68 (8.8%)	18/64 (28.1%)	21/62 (33.9%)
>50-≤75%	2/41 (4.9%)	8/42 (19.0%)	12/39 (30.8%)
>75-100%	0/41 (0.0%)	2/39 (5.1%)	13/43 (30.2%)

Table 15: Test of Significance for Success Rate in the Combined Adult Studies: Percent BSA Affected at Baseline

	P-Value from C chran-Mantel-Haenszel Statistics			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
10-≤25%	<0.001	<0.001	<0.001	0.810
>25-≤50%	0.002	0.004	<0.001	0.495
>50-≤75%	0.011	0.055	0.003	0.231
>75-100%	<0.001	0.137	<0.001	0.004

Table 16: Success Rate in Selected Subsets in Combined Adult Studies

	0.03%	**0.1%**	**P-Value CMH 0.03% vs 0.1%**
Patients in Adult Studies	58/211 (27.5%)	77/209 (36.8%)	0.041
15-64 Years of Age	56/202 (27.7%)	74/197 (37.6%)	0.036
Female	31/116 (26.7%)	50/124 (40.3%)	0.029
Severe AD at Baseline	23/118 (19.5%)	43/123 (35.0%)	0 009
>75-100% BSA at Baseline	2/39 (5.1%)	13/43 (30.2%)	0.004
Black	9/55 (16.4%)	16/55 (29.1%)	0.107

Reviewer's Comments:

The results in Tables 6-15 demonstrate that:

1. The number of subjects more than 64 years in age is very small (9 to 11 in each arm) resulting in failure to show effectiveness of either 0.03% or 0.1% formulations.
2. The 0.03% formulation is not significantly better than vehicle in black patients (n is reasonably adequate) or in patients with more than 75% of the BSA involved at baseline (n is reasonably adequate), or in oriental patients (n is small, 9-12 in each arm).
3. The 0.1% formulation is significantly better than vehicle in all sub-populations tested except patients older than 64 years.
4. As re-summarized in Table 16, the 0.1% formulation is significantly more effective than the 0.03% formulation in the following sub-populations of patients: females, blacks, severe disease and extensive disease involvement (>75% BSA).

C- Success by Study Sites:

There was a statistically significant treatment by center interaction with respect to success rate in study 97-0-035. Table 14.2.2.1.1 (NDA, section 8.1.1.2) shows the success rate at the end of treatment by center for this study. The sponsor attributed this interaction to random variations caused by the small number of patients at each center (p.66 of 1466 of ——— /035 section of the NDA).

Reviewer's Comments:

It was noticed that 3 out of 21 centers had a reversed treatment effect, i.e. the vehicle group had higher success rate than the 0.03% tacrolimus group. This was also observed and analyzed by the statistical reviewer (section V.2). The rate of success ranged from 40 to 50 % in the vehicle group, and from 0 to 20% in the 0.03% group in the efficacy evaluable population in these three centers (NDA, Table 14.2.2.1.1). The statistical reviewer has calculated the corresponding rates in the ITT population (Table 12 of Statistical Review). Further statistical analysis of the demographics of these patients (Table 13 of Statistical Review) did not reveal any meaningful reason for these higher rates in the vehicle group. It is concluded, in agreement with the sponsor, that this is due to random variations caused by the small number of patients enrolled (4 to 6 in each arm, Table 12 of Statistical Review) at each center.

8.3.1.4.2.2 Secondary Efficacy Results

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

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

The change from baseline to the end of treatment in the percentage of affected body surface area in the ITT population of the adult studies (#035 and #036) is presented in the following 2 tables.

Table 17: Change from Baseline to the End of Treatment in the Adult Pivotal Studies: Affected Body Surface Area

Least Square Mean ± SE	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Adult Studies†	N=211	N=211	N=207
Change from Baseline	-5.1 ± 1.23	-18.9 ± 1.23	-24.5 ± 1.25
Study 97-0-035†	N=101	N=103	N=97
Change from Baseline	-6.9 ± 1.81	-19.9 ± 1.79	-22.0 ± 1.85
Study 97-0-036	N=110	N=108	N=110
Change from Baseline	-3.2 ± 1.68	-17.9 ± 1.69	-27.0 ± 1.68

Patient Population: Modified intent-to-treat; all randomized patients who received at least one dose of study drug (= all patients who were dispensed study drug).

† Patient No. 84515 was enrolled/randomized in adult Study 97-0-035 despite being 15 years of age. For all analyses in the ISE except for age-based analyses, this patient is considered an adult patient.

Source: Section 8.3.6 (ISE Statistical Appendix 8.3.6.7.2,4,5).

Table 18: Test of Significance for Change from Baseline in Affected Body Surface Area in the Adult Pivotal Studies

	P-Value from General Linear Model Analysis†			
	Overall	**0.03% vs Vehicle**	**0.1% vs Vehicle**	**0.03% vs 0.1%**
Adult Studies‡	<0.001	<0.001	<0.001	0.001
Study 97-0-035‡	<0.001	<0.001	<0.001	0.422
Study 97-0-036	<0.001	<0.001	<0.001	<0.001

Patient Population: Modified intent-to-treat; all randomized patients who received at least one dose of study drug (= all patients who were dispensed study drug).

† Statistical significance is indicated by p-values ≤0.05.

‡ Patient No. 84515 was enrolled/randomized in adult Study 97-0-035 despite being 15 years of age. For all analyses in the ISE except for age-based analyses, this patient is considered an adult patient.

Source: Section 8.3.6 (ISE Statistical Appendix 8.3.6.7.2,4,5).

Reviewer's Comments:

Statistically significantly greater improvement was observed in the %BSA involved for each tacrolimus ointment treatment group compared with the vehicle group. A statistically significant difference between tacrolimus ointment treatment groups was observed in the adult studies combined, with greater improvement observed for the 0.1% tacrolimus ointment treatment group compared with the 0.03% tacrolimus ointment treatment group.

Improvement was observed as early as Week 1 in both tacrolimus treatment groups. Throughout the study duration, greater decreases in the percentage of affected body surface area were observed for each tacrolimus treatment group compared with the vehicle group (see NDA: ISE Statistical Appendices 8.3.6.8.1, 8.3.6.8.2, 8.3.6.8.3, 8.3.6.8.4, and 8.3.6.8.5).

B- Reduction in physician assessment of individual signs

The Change from Baseline to the End of Treatment for Individual Signs of Atopic Dermatitis (ITT Population) in Protocols # 97-0-035, 97-0-036 (separately and combined), and the results of the test of significance for Individual Signs (ITT Population) in the Combined Adult Protocols # 97-0-035, 97-0-036, are shown in tables 19-A and 19-B, respectively.

Table 19-A: Change from Baseline to the End of Treatment for Individual Signs of Atopic Dermatitis: Intent to Treat Population (Protocols 97-0-035, 97-0-036)

Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Edema			
N (035)	101	103	97
Least Squares Mean ± SE	-0.1 ± 0.07	-0.8 ± 0.07	-0.9 ± 0.07
N (036)	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.06	-0.6 ± 0.06	-0.9 ± 0.06
N (combined)	211	211	207
Least Squares Mean ± SE	-0.1 ± 0.05	-0.7 ± 0.05	-0.9 ±0.05
Erythema			
N (035)	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.07	-0.9 ± 0.07	-0.8 ± 0.07
N (036)	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.06	-0.7 ± 0.06	-0.9 ± 0.06
N (combined)	211	211	207
Least Squares Mean ± SE	-0.2 ± 0.05	-0.8 ± 0.05	-0.9 ± 0.05
Excoriation			
N (035)	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.07	-0.7 ± 0.07	-0.8 ± 0.07
N (036)	110	108	110
Least Squares Mean ± SE	0.0 ± 0.06	-0.6 ± 0.06	-0.8 ± 0.06
N (combined)	211	211	207
Least Squares Mean ± SE	-0.1 ± 0.05	-0.7 ± 0.05	-0.8 ± 0.05
Lichenification			
N (035)	101	103	97
Least Squares Mean ± SE	-0.2 ± 0.06	-0.8 ± 0.06	-0.8 ± 0.06
N (036)	110	108	110
Least Squares Mean ± SE	-0.1 ± 0.05	-0.6 ± 0.05	-0.7 ± 0.05
N (combined)	211	211	207
Least Squares Mean ± SE	-0.2 ± 0.04	-0.7 ± 0.04	-0.8 ± 0.04
Oozing			
N (035)	101	103	97
Least Squares Mean ± SE	-0.1 ± 0.05	-0.4 ± 0.05	-0.4 ± 0.05
N (036)	110	108	110
Least Squares Mean ± SE	-0.0 ± 0.04	-0.2 ± 0.04	-0.3 ± 0.04
N (combined)	211	211	207
Least Squares Mean ± SE	0.0 ± 0.03	-0.3 ± 0.03	-0.4 ± 0.03
Scaling			
N (035)	101	103	97
Least Squares Mean ± SE	-0.4 ± 0.06	-0.8 ± 0.06	-1.0 ± 0.07
N (036)	110	108	110
Least Squares Mean ± SE	-0.3 ± 0.06	-0.8 ± 0.07	-0.9 ± 0.06
N (combined)	211	211	207
Least Squares Mean ± SE	-0.3 ± 0.05	-0.8 ± 0.05	-1.0 ± 0.05

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug. [One patient randomized to vehicle was never dispensed study drug; therefore modified intent-to-treat definition = FDA intent-to-treat definition].
SE: standard error. Source: Integrated Summary of Effectiveness Appendix 8.3.6.7.2,4,5

Table 19-B: Test of Significance for Individual Signs of Atopic Dermatitis: Intent to Treat Population (Combined Adult Protocols # 97-0-035, 97-0-036)

Parameter	General Linear Model Analysis p-Values			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Edema	<0.001	<0.001	<0.001	0.005*
Erythema	<0.001	<0.001	<0.001	0.284
Excoriation	<0.001	<0.001	<0.001	0.046*
Lichenification	<0.001	<0.001	<0.001	0.129
Oozing	<0.001	<0.001	<0.001	0.190
Scaling	<0.001	<0.001	<0.001	0.010*

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug. [One patient randomized to vehicle was never dispensed study drug; therefore modified intent-to-treat definition = FDA intent-to-treat definition]. * Indicates statistical significance at 0.01 or 0.05.
Source: Integrated Summary of Effectiveness Appendix 8.3.6.7.2

Reviewer's Comments:

The sponsor's analysis in each trial report as well as in the ISE was limited to the total of the individual scores, although the proposed label includes [redacted] Therefore, tables 19-A and 19-B had to be compiled by the reviewer from tables in Appendices 8.3.6.7.2, 8.3.6.7.4, and 8.3.6.7.5 of the ISE of the NDA.

The representative score for each of the six clinical signs, edema, erythema, excoriation, lichenification, oozing, and scaling, was defined as the sum of the individual scores for all body regions treated at baseline divided by the number of regions treated at baseline. As shown in tables 19 and 20, the results obtained for each of the six individual signs of atopic dermatitis in the adult studies combined, showed significantly greater improvements in the 0.03% and the 0.1% tacrolimus ointment group compared to the vehicle. Also, the results obtained for each of the six individual signs of atopic dermatitis in each of the the adult studies, showed significantly greater improvements in the 0.03% and the 0.1% tacrolimus ointment group compared to the vehicle (Table 19-A in this review, and Appendices 8.3.6.7.4, and 8.3.6.7.5 of the ISE of the NDA).

Comparison of the 0.1% tacrolimus ointment group with the 0.03% tacrolimus ointment group showed significant differences in the representative scores for edema (p=0.005), excoriation (p=0.046), and scaling (p=0.010) (Table 19-B).

C- *Patient's assessment of treatment effects*

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

The results of the patient's assessment of overall response were presented in the NDA, section 8.3.6 (ISE Statistical Appendices 8.3.6.6.2, 8.3.6.6.4 and 8.3.6.6.5) for the two adult studies combined, and for each of the adult studies, respectively. These results were discussed in the NDA section 8.3.3.9 (ISE) and were summarized in table 25 of this section. Statistically significant differences were observed among treatment groups for the adult studies combined ($p<0.001$ for each; CMH statistics testing for row mean score difference); statistically significant differences between each tacrolimus ointment group and vehicle were also observed ($p<0.001$ for each). No statistically significant differences were observed between 0.1% tacrolimus ointment and 0.03% tacrolimus.

Reviewer's Comments:

The results of the patient's assessment of overall response are in general agreement with the primary efficacy variable except for their failure to show a statistically significant difference between the two concentrations of tacrolimus ointment.

The following table of the change in patient's assessment of pruritus has been compiled by the reviewer from the NDA statistical appendices 8.3.6.7.2, 8.3.6.7.4 and 8.3.6.7.5 (ISE).

Table 20: Change from Baseline to the End of Treatment for Patient's Assessment of Pruritus: Intent to Treat Population in Adult Studies

Change from Baseline	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Protocol 97-0-035			
N	100	102	95
Least Squares Mean ± SE	-0.7 ± 0.31	-3.8 ± 0.30	-3.6 ± 0.31
Protocol 97-0-036			
N	107	107	109
Least Squares Mean ± SE	-0.6 ± 0.29	-3.1 ± 0.29	-3.5 ± 0.29
Protocols 97-0-035 and -036 combined			
N	207	209	204
Least Squares Mean ± SE	-0.7 ± 0.21	-3.4 ± 0.21	-3.5 ± 0.21

Patient population: Intent-to-treat = modified intent-to-treat = all randomized patients who received at least one dose of study drug. [One patient randomized to vehicle in trial 97-0-035 was never dispensed study drug; therefore modified intent-to-treat definition = FDA intent-to-treat definition].
Source: Integrated Summary of Effectiveness Appendix 8.3.6.7.2,4,5.

The differences between the 0.03% or the 0.1% tacrolimus ointments and the vehicle were statistically significant in each trial as well as in the combined trials, but the differences between the 0.03% and the 0.1% tacrolimus ointments were not statistically significant in any of them.

D- Recurrences

Reviewer's Comments:

Although recurrences were one of the secondary efficacy variables, they were not discussed by the sponsor in the individual study reports or in the ISE. The data, however, were presented in tables 14.3.5.6.1 in the statistical appendix of the reports on the individual studies. The number of patients in the adult studies combined (97-0-035 and –036) 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. This information is recommended for inclusion in the label.

8.3.2 Trial #3: FG-06-12

8.3.2.1 Objective/Rationale

The primary objective of this study was to assess the safety of tacrolimus ointment when used continuously or intermittently for either 6 or 12 months in adult patients with moderate to severe atopic dermatitis. In addition, long-term efficacy was evaluated based on patient's and physician's assessments.

8.3.2.2 Design

This was a phase 3, open-label, single-concentration (0.1%), multi-center, long-term study. Assessments for efficacy were performed on Day 1 (baseline), Weeks 1 and 2, once a month thereafter, and on unscheduled visits. Adverse events were monitored on an ongoing basis. Laboratory tests and blood pressure measurements were carried out at the time of screening in addition to the visits used to assess efficacy. CD_4 and CD_8 counts were carried out on Day 1 and Months 1, 3, 6 and 12. The Recall Antigen Test (an assessment of cell-mediated immunity) was carried out on Day 1 and Months 6 and 12 at selected centers. Tacrolimus concentrations in whole blood were assessed on Day 1, Weeks 1 and 2, Months 1 and 3, and the last visit.

Reviewer's Comments:

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

8.3.2.3 Study Results

8.3.2.3.1 Long-term Efficacy

In this study, 246 patients were on study for at least 6 months and 68 patients were on study for 12 months. The efficacy parameters for this long-term study are presented by study visit in the NDA, ISE, section 8.3.6 (ISE Statistical Appendicx 8.3.6.9.2).

In this study, patients showed a rapid improvement (within 1 week) in their disease status. Improvement was evidenced by reductions in the percent body surface area affected, EASI score, modified EASI score, and Patient's Assessment of Itch; improvement was also observed for the Patient's and Physician's Assessment of Global Response. Improvement of atopic dermatitis was apparent after one week of treatment with 0.1% tacrolimus ointment and maximal improvement (Month 3) was maintained for the remainder of the study. There was no evidence of loss of effectiveness over time.

Table 21: Efficacy Variables By Visit: Adult Study FG-06-12 (European Long-term Study)

Parameter	N	Mean ± SE	N	Change from Baseline (Mean ± SE)
% BSA Affected				
Day 1	316	34.7 ± 1.0	—	—
Week 1	302	28.6 ± 1.1	302	-5.8 ± 0.7
Month 3	282	15.2 ± 1.0	282	-19.5 ± 1.0
Month 6	237	12.8 ± 1.0	237	-21.5 ± 1.3
Month 12	66	11.7 ± 1.8	66	-23.8 ± 2.0
EASI Score				
Day 1	316	18.2 ± 0.6	—	—
Week 1	302	10.7 ± 0.5	302	-7.3 ± 0.4
Month 3	280	5.7 ± 0.4	280	-12.3 ± 0.5
Month 6	237	4.9 ± 0.5	237	-13.0 ± 0.7
Month 12	66	5.1 ± 0.8	66	-14.1 ± 1.2
Modified EASI Score				
Day 1	300	23.7 ± 0.7	—	—
Week 1	302	13.5 ± 0.6	287	-9.7 ± 0.6
Month 3	278	7.3 ± 0.6	266	-16.2 ± 0.7
Month 6	236	6.1 ± 0.6	226	-16.9 ± 0.9
Month 12	66	6.1 ± 1.0	59	-17.9 ± 1.5
Patient's Assessment of Itch				
Day 1	300	5.9 ± 0.2	—	—
Week 1	302	3.5 ± 0.2	287	-2.3 ± 0.2
Month 3	279	2.6 ± 0.2	267	-3.3 ± 0.2
Month 6	236	2.1 ± 0.2	226	-3.7 ± 0.2
Month 12	66	1.8 ± 0.3	59	-3.8 ± 0.4

Patient Population: all enrolled patients who received at least one dose of study drug and had post-baseline data. SD: standard deviation. BSA: body surface area.
EASI: Eczema Area and Severity Index; composite of severity grade in Physician's Assessment for four individual signs and adjusted percentage of affected body surface area. Highest possible score is 72.
Modified EASI is a composite of the EASI and the patient's assessment of itch. Highest possible score is 90.
Source: NDA, ISE, Table 27; and section 8.3.6 (ISE Statistical Appendix 8.3.6.9.2).

Reviewer's Comments:

The results presented in Table 21 show maintenance, or slowly progressive improvement, of the averages of measurements indicative of effective treatment of the atopic dermatitis patients over 6 and 12 months of treatment. However, no data were presented or discussed, either in the individual study report or the ISE, regarding recurrence or relapse rates. The protocol included provisions for unscheduled visits if the patient experienced a severe flare-up of atopic dermatitis or other medical problem (to be discussed with safety), but not for a gradual recurrence.

As a measure of the long-term effectiveness of treatment, relapse or recurrence rates may be indicated by the days of treatment, the usage of the ointment, or the %BSA treated at different times. Tables for these parameters were provided in the appendix of the study report (tables 13.3.1-4). The protocol of this study allowed patients to change the treatment areas or select new ones on the basis of the presence of itch, although the initial treatment area (maximal set to 60% BSA) was selected by the investigator on day 1. Also, patients were instructed to continue application of the ointment for one week after itch had resolved. The treated areas could extend up to 100% of the BSA and the ointment usage could extend to a maximum of 30 g/day (see NDA, section 8.2.1.2, treatment administration [section 5.3.1]).

The results presented in these tables (NDA, section 8.2.1.2, tables 13.3.1-4) show a general decrease in total treated BSA and the ointment use per application day from week 1 to month 2. This was maintained or slightly improved up till month 12 (tables 13.3.3&4). Table 13.3.1 shows that the 6 month group of patients were without treatment for **13.4%** of the total days they were in the study (21.8/159.1), and the patients in the 12 month group were without treatment for **14.1%** of the total days they were in the study (48.5/317.2). This information was based on the patients' diaries, and the days when the information was missing, it was assumed that the patient has applied treatment (14.4% in 6 month group, and 10.3% in 12 month group).

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

8.4 Review of efficacy: Indication #2

Treatment of atopic dermatitis in children

8.4.1: Trial #1: 97-0-037

8.4.1.1 Objective/Rationale

This study was designed to determine the safety and demonstrate the efficacy of topically applied tacrolimus ointment (0.03% or 0.1%) in treating the signs and symptoms of moderate to severe atopic dermatitis involving at least 10% of the body surface area in pediatric patients (2-16 years of age).

8.4.1.2 Design

This pivotal study was designed similar to the two pivotal adult studies 97-0-035 and –036 with respect to objective, procedures, treatment duration, endpoints and analyses. It was a randomized, double-blind, parallel group, three-arm, vehicle-controlled, multicenter study. There were 23 centers in the United States (24 investigators) in this study. Patients applied a thin coat of tacrolimus ointment (0.03% or 0.1%) or vehicle twice daily (q10-14 hours) to areas of active disease as defined by the investigator at the baseline visit. The maximum duration of treatment was 12 weeks. In patients with clearing of atopic dermatitis, treatment was to have continued for 1 week after clearing. There was a 2-week follow-up visit after treatment discontinuation.

Patients were evaluated at baseline; during treatment (Weeks 1, 2, 3, 6, 9); at Week 12 or end of treatment, if earlier; and at the end of the study (2 weeks posttreatment/Week 14). Adverse events were recorded through 2 weeks posttreatment. The primary efficacy endpoint was the incidence of success obtained from the Physician's Global at the end of treatment. Success was defined as a rating of cleared or excellent improvement (90-100% improvement in areas defined for treatment at baseline). Secondary endpoints included EASI score, percent of body surface area affected, Physician's Assessment of Individual Signs of Atopic Dermatitis, and Patient's Assessment of Pruritus.

The primary patient population for efficacy analyses as prospectively defined in the analysis plan was the evaluable patient subset comprised of all randomized patients who received study drug for at least 3 consecutive days (minimum of five applications) beginning at baseline and had at least one "on treatment" value for the Physician's Global. However, at the pre-NDA meeting in April 1999, the FDA requested the primary patient population for efficacy analyses be the intent-to-treat population (ITT), all randomized patients who were dispensed the treatment medication. For this study, the ITT population is identical to the modified intent-to-treat population (MITT) presented in the study report (all randomized patients who received at least one dose of study drug), since the only randomized patient who did not receive at least one dose of study drug (in the vehicle arm of the study) was not dispensed study drug (i.e., ITT = MITT).

Cochran-Mantel-Haenszel test stratified by age group was performed to determine if there was a statistically significant difference in the success rate among the three treatment groups. Since statistical significance at the 5% level was obtained in this study, Cochran-Mantel-Haenszel test stratified by age group was used for the pairwise comparison of the three treatment groups, each at the 5% level of significance.

8.4.1.3 Protocol Overview

8.4.1.3.1 Population, procedures

The patient's eligibility for the study was determined based on an informational interview, an examination to confirm the diagnosis of atopic dermatitis and its severity, and the results of a

urine pregnancy test (if female with child-bearing potential). Written informed consent was obtained prior to enrollment in the study.

Inclusion Criteria

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 [Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Dermatov 1980;Suppl 92:44-7.] (for details see: Appendix 14.1.1, protocol)
- moderate to severe atopic dermatitis based on the Rajka and Langeland grading system [Rajka G, Langeland T. Grading of the severity of atopic dermatitis. Acta Derm Venereol (Stockh) 1989;Suppl 144:13-4.] involving at least 10% of the body surface area (for details see: Appendix 14.1.1, protocol)
- at least 2 years of age but less than 16 years of age
- parent/legal guardian (and patient, if applicable), provided written informed consent
- agreement by patient or parent/legal guardian 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 (see Appendix 14.1.1, protocol, for a detailed description and specific washout time frames)
- if female with child-bearing potential (menstruating), a negative pregnancy test
- agreement by patient or parent/legal guardian, if applicable, to comply with study requirements and to come to the clinic for required visits

Exclusion Criteria

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

Overview of Schedule of Procedures

The schedule of study procedures, including an evaluation flow chart, can be found in Appendix 14.1.1, protocol. Patients were evaluated at baseline/Day 1; during treatment (Weeks 1, 2, 3, 6, 9); Week 12 or end of treatment, if earlier; and at the end of the study (2 weeks posttreatment/Week 14). Additional evaluation visits were conducted if necessary. Adverse events were recorded from Day 1 through 2 weeks posttreatment. Blood was collected by venipuncture from patients at six centers on Day 1, Week 1, Week 3 and Week 12/end of treatment in order to determine laboratory profiles.

To aid in data collection, patients or parents/guardians were asked to record drug application information, deviations from instructions, the use of concomitant medications and any symptoms, complaints, illnesses or accidents in a diary throughout the study. These entries were reviewed at scheduled visits and relevant information transferred to the case report form. At six centers, photographs were taken during the study to document disease status.

The efficacy and safety variables in this study are those commonly used in studies of this type and are briefly described in the following subsections; refer to Appendix 14.1.1, protocol, for a detailed presentation of assessments and grading systems.

8.4.1.3.2 Endpoints defined

Efficacy

Optimally, all the physician-based efficacy assessments should have been performed by the same physician rater. However, a secondary ("backup") rater may have performed assessments in the event of an emergency or unavailability of the physician for any of the postbaseline visits. This secondary rater was required to have been present at the baseline evaluation and to have agreed with the primary rater on the baseline ratings.

At each visit, patient assessments were made prior to the physician assessments in order to avoid bias.

Primary Efficacy Endpoint

The primary efficacy endpoint was the incidence of success obtained from the Physician's Global at the end of treatment. For the Physician's Global, changes in the overall status of the atopic dermatitis lesions identified for treatment at baseline were rated using the same scale as in the adult studies (see section 8.3.1.3.2 of this review). Success was defined as a rating of cleared or excellent improvement (i.e., ≥90% improvement in the areas defined for treatment at baseline).

Secondary Efficacy Endpoints

Secondary efficacy endpoints included the change from baseline to the end of treatment for the Eczema Area and Severity Index (EASI), percentage of body surface area affected (% BSA), the Physician's Assessment of Individual Signs of Atopic Dermatitis, the Patient's Assessment of Treatment Effects (Overall Response and Pruritus), and the incidence of recurrence. In addition, the Area under the Curve (AUC) for the Physician's Global and the Patient's Assessment of Overall Response scores over time, standardized by dividing by the total number of treatment days, were calculated by the trapezoidal rule.

Eczema Area and Severity Index (EASI)

This was based on the same parameters and procedures that has been previously described in the adult studies (see section 8.3.1.3.2 of this review). The only difference was in the equation used for calculating the total EASI score, which depended on the patient's age.

The Total EASI score was calculated based on one of the following equations:

1- For patients under the age of 7 years -

$$\text{SCORE} = (\textit{[head/neck TG X AS]} \times 0.2) + (\textit{[upper limbs TG X AS]} \times 0.2) + (\textit{[trunk TG X AS]} \times 0.3) + (\textit{[lower limbs TG X AS]} \times 0.3)$$

2- For patients at least 7 years of age-

$$\text{SCORE} = (\textit{[head/neck TG X AS]} \times 0.1) + (\textit{[upper limbs TG X AS]} \times 0.2) + (\textit{[trunk TG X AS]} \times 0.3) + (\textit{[lower limbs TG X AS]} \times 0.4)$$

It is to be noted that the equation for patients at least 7 years of age is identical with the equation used in the adult studies, and that the highest possible score is 72 at all ages.

Patient's Assessment of Overall Response

At each visit, the patients or parents/guardians provided their perception of the change from baseline in overall (global) disease (e.g., how the atopic dermatitis looked, how it felt, how others reacted to it). Change from baseline was assessed as: "Much Better", "Better", "Slightly Better", the "Same", "Slightly Worse", "Worse", or "Much Worse". Patient's assessments were made prior to the physician's assessments.

Patient's Assessment of Pruritus

The amount and intensity of pruritus experienced during the previous 24-hour period was assessed using a 10 cm visual analog scale where 0 cm = "No Itch" and 10 cm = "Worst Itch Imaginable."

Recurrence

Recurrence was defined as the reappearance or worsening of atopic dermatitis in the baseline defined treatment areas which warranted therapy with the study medication. All patients considered by the investigator to be treatment successes at the end of treatment who subsequently experienced a recurrence during the posttreatment period were to be assessed with respect to EASI score, percent affected body surface area, Physician's Assessment of Individual Signs of Atopic Dermatitis, and Patient's Assessment of Pruritus. The investigator also documented the date of recurrence.

Additional Efficacy Assessments

Additional efficacy assessments included the distribution of responses in the Physician's Global (described above, in section on EASI score) at end of treatment and through Week 3, and the time to first improvement in Physician's Global (at least excellent improvement, at least marked improvement, at least moderate improvement, at least slight improvement; for details see Appendix 14.2.1).

Safety

Safety was assessed based on the incidence of adverse events and changes from baseline in clinical laboratory profile. An adverse event (AE) was defined as any undesirable experience occurring to a patient during the clinical trial whether or not considered related to the study medication. Such occurrences could have been new (emerging during the study) or have represented a worsening of an existing medical condition. All adverse events through 2 weeks posttreatment, whether ascertained through patient interview or parent/guardian interview, physical examination, laboratory findings, or other means, were recorded. In order to better assess the adverse event experience in this study, adverse events were categorized as application site events and nonapplication site events at the time of data collection.

A serious adverse event was defined as any experience that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or congenital anomaly/birth defect, or was considered an important medical event. All serious adverse events were to be immediately reported by telephone or facsimile, followed within 72 hours by a written description of the circumstances surrounding the event, to the Fujisawa Healthcare, Inc. monitor or designee.

Laboratory profiles were determined for 25% of enrolled patients (all patients at six centers). Laboratory parameters included:

- Hematology - hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, eosinophil count (manual count), and platelet count
- Chemistry - sodium, potassium, chloride, blood urea nitrogen, serum creatinine, direct and total bilirubin, transaminases (SGOT/AST; SGPT/ALT), alkaline phosphatase, lactate dehydrogenase, gamma glutamyl transpeptidase, glucose, uric acid, magnesium, IgE
- Urine pregnancy test for female patients (baseline and end of treatment only)

Other: Quality of Life Measurement

The Children's Dermatology Life Quality Index (CDLQI) was used to assess the physical and psycho-social aspects of the disease state [Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. Br J Dermatol 1995;132:942-9.]. With the developer's approval, CDLQI was modified to include a version of the questionnaire designed for toddlers (age 2-4 years). Patients or parents/guardians completed the age specific (2-4 years of age or 5-15 years of age) questionnaire before the physician's assessments (in order to avoid bias) at baseline, Week 3 and Week 12/End-of-Treatment. Either patients or parents/guardians could have completed the questionnaire; however, whoever completed the questionnaire at baseline was to have completed all subsequent questionnaires. CDLQI scores were evaluated by [redacted] a commercial group [redacted] the results are presented in a separate report.

8.4.1.4 Study Results

8.4.1.4.1 Demographics

The patient disposition and population subsets are summarized in Table 22 and Table 23.

Table 22: Patient Disposition [1]

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized :	117	117	118	352
Intent-to-Treat	116	117	118	351
2-6 years	72	74	69	215
7-15 years	44	43	49	136
Completed Treatment	*51 (44.0%)*	*94 (80.3%)*	*101 (85.6%)*	*246 (70.1%)*
Discontinued	*65 (56.0%)*	*23 (19.75)*	*17 (14.4%)*	*105 (29.9%)*
Lack of Efficacy	*46*	*4*	*5*	*55 (15.7%)*
Adverse Event	*9*	*6*	*3*	*18 (5.1%)*
Administrative	*10*	*13*	*9*	*32 (9.1%)*

(1) Source: Tables 1 and 2 of the results section of the study reports, calculated by M.O.

Of note, 56% (65/116) of vehicle-treated patients discontinued the study due to lack of efficacy compared with 20% (23/117) of 0.03% tacrolimus ointment-treated patients and 14% (17/118) of 0.1% tacrolimus ointment-treated patients.

Table 23: Patient Populations

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized	117	117	118	352
Modified 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*
Efficacy Evaluable	101 (86.3%)	108 (92.3%)	107 (90.7%)	316 (89.8%)
2-6 years of age	*63*	*67*	*62*	*192*
7-15 years of age	*38*	*41*	*45*	*124*
Per Protocol Population	83 (70.9%)	91 (77.8%)	100 (84.7%)	274 (77.8%)
2-6 years of age	*47*	*56*	*57*	*160*
7-15 years of age	*36*	*35*	*43*	*114*

Modified intent to-treat population (MITT): all randomized patients who received at least one dose of study drug.
Efficacy evaluable population: all randomized patients who received study drug for at least 3 consecutive days (minimum five applications) beginning on Day 1 and had at least one "on treatment" value for the Physician's Global.
Per protocol population: all randomized patients who completed the study without a major protocol deviation as determined during a blinded patient classification review (see also Appendix 14.2.1).
Source: Tables 13.1.1, 13.2.1.1, and 13.4.1.1, and Appendix 14.3.2.1.1.

Reviewer's Comments:

APPEARS THIS WAY
ON ORIGINAL

Patient demographics and other baseline characteristics of the MITT (=ITT) population are presented in Appendices 14.3.2.1, 14.3.2.2, and 14.3.2.3. Listings by patient number are found in Appendices 14.4.1.2, 14.4.1.3, and 14.4.1.4 of the respective study reports.

No statistically significant differences among treatment groups were observed for any demographic or baseline characteristics for the ITT population or for the either age group (2-6 and 7-15 years) within the population.

The treatment groups and patient populations were balanced with respect to age (61.3% 2-6 years, mean = 6.1), race, and gender (47% male). The majority of patients were white (65.2%); however, blacks were well represented, comprising a little more than a quarter of the patients (26.8%), and approximately half (47.7%) of the patients' total body surface area was affected at baseline, with more than 80% of patients being affected in the head/neck region. The majority of patients (61.5%) had severe atopic dermatitis.