Tacrolimus Ointment
(0.03% and 0.1%)

NDA 50-777

In the Treatment of the Signs and Symptoms of Atopic Dermatitis
In Pediatrics (2 to 15 years of age) and Adults

Briefing Document
for Dermatologic and Ophthalmic Drugs
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This document is only for the use of the FDA, their consultants and members of the Dermatologic and Ophthalmic Drugs Advisory Committee.

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1 EXECUTIVE SUMMARY

Atopic dermatitis is an intensely pruritic, recurring inflammatory skin disease which can significantly impact a patient's health and life. Current therapeutic options for atopic dermatitis (e.g., topical steroids, systemic steroids, PUVA, etc.) carry such potential risks as skin atrophy, hypopigmentation, striae, telangiectases, secondary infections, acne, skin hemorrhage after minor trauma, hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation, and cutaneous malignant lesions. Patients treated with current therapies often have to take "drug holidays" to minimize the risk of side effects. These holidays can lead to frequent flares and complications like skin infections. In current practice, patients with resistant disease undergoing topical steroidal therapy often require periodic systemic steroidal pulses or other concomitant medication which increases their risk for adverse events.

1.1 Indication

Tacrolimus ointment was developed specifically for the treatment of atopic dermatitis and represents the first in a new class of topical, nonsteroidal immunomodulators. The proposed indication for tacrolimus ointment (0.03% and 0.1%) is primary therapy for the short-term and long-term treatment of the signs and symptoms of atopic dermatitis in adult and pediatric patients 2 years of age or older.

1.2 Global Program

The tacrolimus ointment global development program included a total of 4,194 patients/healthy volunteers in 28 studies conducted in the United States, Europe, or Japan. Of these individuals, 2,847 atopic dermatitis patients applied tacrolimus ointment at concentrations ranging from 0.03% to 0.5% in 20 Phase 2 or 3 clinical studies and were evaluable for safety. The safety profile for these 20 studies was comparable to that observed for the five Phase 3 studies which formed the core of NDA 50-777.

1.3 Pharmacology

In studies in healthy volunteers, tacrolimus ointment was shown to be neither phototoxic, photoallergenic, nor a contact sensitizer. Tacrolimus ointment is minimally absorbed through damaged skin; absolute bioavailability is <0.5%. There is no evidence of systemic accumulation. In clinical studies, quantifiable tacrolimus blood concentrations following topical application were isolated events, generally observed early in treatment. In three US Phase 3, 12-week double-blind studies in children and adults and one long-term safety study in adults conducted in the EU, the highest individual tacrolimus blood concentration was ≥ 5 ng/mL in 0.5% (4/754) of patients; these few patients did not experience this concentration for a prolonged period but only at a single sampling time and in one blood sample.

The adverse event profile of patients with a quantifiable tacrolimus blood concentration at any time during treatment was generally consistent with that of patients without quantifiable levels.

1.4 Identification of Core Studies

It was agreed at the end-of-Phase 2 meeting between Fujisawa Healthcare, Inc. and the FDA (October 28, 1996) that five core studies would be adequate to support the indication (primary therapy for the short-term and long-term treatment of atopic dermatitis). Although data were presented in NDA 50-777 for all 28 studies in the global program, the submission and the briefing document focus on the five core studies for efficacy and safety conclusions. The core studies are:

- *Three 12-Week, Double-Blind Studies:* Three multicenter, randomized, double-blind, vehicle-controlled 12-week studies conducted in the United States; one in pediatric patients (Study 97-0-037) and two in adult patients (Studies 97-0-035 and 97-0-036) evaluating the 0.03% and 0.1% tacrolimus ointment concentrations.
- *Two Long-Term Safety Studies:* Two multicenter, open-label, single concentration (0.1% tacrolimus ointment), long-term (up to 12 months) studies; one conducted in the United States in pediatric patients (Study 96-0-025) and one conducted in Europe in adult patients (Study FG-06-12). [Note: These were not extension patients from shorter duration studies.]

1.5 Patient Population in Core Studies

A total of 1,556 patients with moderate or severe atopic dermatitis have been treated in the five core studies. The population evaluated in these studies is representative of the atopic dermatitis population seeking treatment. Of the 607 pediatric (<16 years of age) patients evaluated in the core studies, 330 were 2 to 6 years of age. The extent of body surface area (BSA) affected at baseline varied from 2% to 100%, with most patients affected over more than one-third of their body surface area. Eighty-six percent of patients treated the head/neck region. The core studies' population had an adequate gender and racial representation, with nearly an equal percentage of males and females and a substantial (~22%) representation for African Americans.

1.6 Study Drug Application in Core Studies

Patients applied a thin layer of study drug (0.03% or 0.1% tacrolimus ointment, or vehicle in 12-week studies; 0.1% tacrolimus ointment in long-term safety studies) twice daily to areas of active disease as defined by the investigator at the baseline visit. Patients treated all affected areas (including head, neck, intertriginous areas) unless, in

the physician's judgment, it was in the best interest of the patient to exclude a small portion from treatment. The protocol recommended a 1 cm ribbon spread over approximately 100 cm^2 skin surface. In patients with clearing of atopic dermatitis, treatment was to have continued for 1 week after clearing. Patients were allowed to treat new lesions if they developed.

1.7 Efficacy

1.7.1 Primary Efficacy Endpoint

In each of three 12-week double-blind studies, the primary efficacy endpoint was the incidence of success (≥ 90% improvement) obtained from the Physician's Global Evaluation of Clinical Response (Physician's Global) at the end of treatment. In each of the three pivotal studies, an overall test among the three treatment groups was performed. Since that was statistically significant in each study, each pairwise comparison was performed. The primary pairwise comparison involved each tacrolimus ointment concentration versus vehicle. The secondary pairwise comparison was the 0.1% tacrolimus ointment concentration versus the 0.03% concentration. These analyses were then performed for data from the three studies combined and, using combined data, for subsets of the population.

In each of three 12-week double-blind studies, and when data from these studies were combined, both concentrations of tacrolimus ointment had a statistically significantly higher success rate than vehicle. The success rate was 4- to 5-fold higher in tacrolimus ointment-treated patients compared with vehicle-treated patients.

Table 1: Executive Summary: Primary Efficacy Variable: Success Rate (³ 90% Improvement) At The End Of Treatment

Study	Treatment Group			
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Pediatric Study 97-0-037	8/116 (6.9%)	42/117 (35.9%)	48/118 (40.7%)	
Adult Study 97-0-035†	8/102 (7.8%)	30/103 (29.1%)	35/99 (35.4%)	
Adult Study 97-0-036	6/110 (5.5%)	28/108 (25.9%)	42/110 (38.2%)	
Adult Studies Combined	14/212 (6.6%)	58/211 (27.5%)	77/209 (36.8%)	
All Studies Combined	**22/328 (6.7%)**	**100/328 (30.5%)**	**125/327 (38.2%)**	
	p-Value §			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Pediatric Study 97-0-037	<0.001	<0.001	<0.001	0.401
Adult Study 97-0-035†	<0.001	<0.001	<0.001	0.369
Adult Study 97-0-036	<0.001	<0.001	<0.001	0.060
Adult Studies Combined	<0.001	<0.001	<0.001	0.041
All Studies Combined	**<0.001**	**<0.001**	**<0.001**	**0.038**

Population: intent-to-treat; all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug).
† Patient No. 84515 was enrolled/randomized in adult Study 97-0-035 despite being 15 years of age. §P-values for patients in pediatric study are from Cochran-Mantel-Haenszel statistics stratified by age. For individual study results for Studies 97-0-035 and 97-0-036, p-values are from Fisher's exact test. Statistical significance is indicated by p-values ≤0.05. For combined results, p-values are from Cochran-Mantel-Haenszel statistics stratified by study.
Success = cleared or excellent improvement (≥90% improvement) based on Physician's Global.

The success criterion used in these studies is stringent. Also clinically relevant is at least moderate improvement (≥ 50% improvement). Results using this criterion confirmed those using the more stringent success criterion. Clinically relevant improvement was rapid as shown in the following table. About 50% of tacrolimus-treated patients had at least moderate improvement (≥50% improvement from baseline) at the Week 1 visit compared with only 17% of vehicle-treated patients.

Table 2: Executive Summary: At Least Moderate (³50%) Improvement From Baseline

Visit	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Week 1	16.8%	45.7%	54.0%
End of Treatment	22.3%	65.5%	74.6%
p<0.001, Vehicle versus 0.03% or 0.1% tacrolimus ointment at end of treatment			
p=0.011, 0.1% versus 0.03% tacrolimus ointment at end of treatment			

Patient Population: intent-to-treat; all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug).
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult) combined.

1.7.2 Secondary Endpoints

Results of analyses of secondary endpoints (EASI score, Physician's Assessment of Individual Signs of Atopic Dermatitis [Total Score as well as Representative Score for each sign], %BSA affected, and Patient's Assessment of Pruritus) confirmed the primary endpoint results. Improvement in these secondary parameters generally occurred during the first week of treatment.

Based on the results of two long-term (up to 1 year) safety studies, there is no suggestion of a loss of the effectiveness of tacrolimus ointment over time.

1.8 Safety

In three 12-week, double-blind studies, the overall incidence of adverse events, nonapplication site adverse events and infections were comparable between vehicle and each tacrolimus ointment concentration. There was no evidence of an increased risk for adverse events when tacrolimus ointment was applied to the head and neck compared with application to other areas of the body.

The use of tacrolimus ointment may cause local symptoms of short duration such as a sensation of skin burning or pruritus. These localized symptoms are most common during the first few days of application and typically resolve as lesions heal. Other events with a higher 12-week adjusted incidence rate in a tacrolimus ointment group compared with the vehicle group in the 12-week, double-blind studies included:

- For 0.1% tacrolimus ointment compared with vehicle- flu-like symptoms (31% vs 22%), headache (17% vs 10%), acne (5% vs 1%), cyst (2% vs 0), dyspepsia (3% vs 1%), skin tingling (5% vs 2%), and hyperesthesia (4% vs 1%; e.g., generally localized sensitivity to temperature);
- For 0.03% tacrolimus ointment versus vehicle-herpes zoster (2% vs 0; 5 of 6 cases were chicken pox in pediatric patients); and
- For both the 0.03% concentration and the 0.1% concentration versus vehicle-folliculitis (5%, 3%, respectively vs 1%), alcohol intolerance (2%, 4% respectively vs 0; flushing, redness after alcohol consumption), and myalgia (2%, 1% respectively vs 0).

Hazard rates analyses demonstrated that there is no evidence of increased risk of adverse events over time, even with long-term use of 0.1% tacrolimus ointment.

1.9 Quality of Life

Age-specific quality of life questionnaires (Children's Dermatology Life Quality Index, children 5 to 15 years of age; modified version, toddlers 2 to 4 years of age; and Dermatology Life Quality Index, adults ≥16 years of age) were completed by patients/parents/guardians in the three 12-week, double-blind studies. Compared with those applying vehicle, patients treated with 0.03% or 0.1% tacrolimus ointment had significantly more quality of life benefits in the areas of symptoms and feelings, everyday activities, personal relationships, sleep, and treatment impact. In children, the most substantial improvements were in the areas of sleep, and symptoms and feelings.

1.10 Two Concentrations: 0.1% Versus 0.03% Tacrolimus Ointment

In each individual Phase 3, 12-week double-blind study, the success rate was numerically higher for the 0.1% tacrolimus ointment group compared with the 0.03% concentration group. This result was consistent across all three studies.

Data from the three 12-week double-blind studies combined demonstrate that the 0.1% tacrolimus ointment concentration provided a greater therapeutic benefit than the 0.03% tacrolimus ointment concentration as evidenced by a statistically significantly higher success rate, a statistically significantly more favorable distribution of improvement ratings for the Physician's Global, and statistically significantly better scores for edema, excoriation, and scaling, % BSA affected and EASI score. The greater therapeutic benefit of 0.1% tacrolimus ointment compared with the 0.03% concentration was particularly evident in adult patients, and patients with severe atopic dermatitis at baseline and those with extensive disease involvement

Table 3: Executive Summary: Success (³ 90% Improvement) Rate At The End Of Treatment: Subsets of Interest

	0.03%	0.1%	p-Value CMH† 0.03% vs 0.1%
Patients in All Studies	100/328 (30.5%)	125/327 (38.2%)	0.038
Severity of AD at Baseline			
Moderate	55/138 (39.9%)	54/129 (41.9%)	0.839
Severe	45/190 (23.7%)	71/198 (35.9%)	0.010
% Affected BSA at Baseline			
≥10% - ≤25%	48/107 (44.9%)	42/92 (45.7%)	0.960
>25% - ≤50%	29/91 (31.9%)	40/98 (40.8%)	0.266
>50% - ≤75%	18/70 (25.7%)	26/73 (35.6%)	0.246
>75% - 100%	5/60 (8.3%)	17/64 (26.6%)	0.010

Patient Population: intent-to-treat; all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug). Success = cleared or excellent improvement (≥90% improvement) based on Physician's Global.
AD: Atopic dermatitis. BSA: Body surface area affected by atopic dermatitis. Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult). † CMH: Cochran-Mantel-Haenszel Statistics stratified by study. Statistical significance is indicated by p-values ≤0.05.

The data also suggest a greater therapeutic benefit with the 0.1% tacrolimus ointment concentration compared with the 0.03% concentration for African American adults.

No adverse event had a statistically higher incidence in the 0.1% tacrolimus ointment group compared with the 0.03% concentration. There was no difference in laboratory profile in the two tacrolimus ointment concentration groups.

In adults, statistically significantly greater improvements in the quality of life were observed in patients treated with the 0.1% tacrolimus ointment concentration compared with those treated with the 0.03% tacrolimus ointment concentration.

1.11 Summary

- Both concentrations of tacrolimus ointment evaluated (0.03% and 0.1%) are more effective than vehicle in the treatment of atopic dermatitis in adult and pediatric patients.

- Clinical response is rapid, generally within 1 week.

- Quality of life is improved.

- Both concentrations of tacrolimus ointment are effective additions to the physician's armamentarium for the treatment of atopic dermatitis. The availability of both concentrations provides physicians with a needed therapeutic flexibility so that they may tailor treatment to patient needs.

- The 0.1% tacrolimus ointment concentration may be particularly beneficial for adults, those with severe disease, those with extensive body surface area involvement, and African American adults.

- Both concentrations of tacrolimus ointment can be safely used on the head, neck and other body regions including intertriginous areas.

- Both concentrations of tacrolimus ointment can be safely used in children as young as 2 years of age.

- When tacrolimus ointment is applied for up to 1 year, there is no suggestion of a loss of effectiveness and no increased risk for adverse events.

2 INTRODUCTION

2.1 Standard of Care

Atopic dermatitis is an intensely pruritic, recurring inflammatory skin disease which can significantly impact a patient's health and life, hindering social interaction, lowering self-esteem, leading to work/school absenteeism, negatively affecting family interactions, and producing sleep disturbances and emotional distress [1, 2, 3, 4].

Standard therapeutic modalities, directed at controlling the predominant symptoms of atopic dermatitis (e.g., erythema and pruritus), include the liberal use of emollients, minimizing contact with irritants, dietary intervention, antihistamines, antibiotics, and topical corticosteroids. Topical corticosteroids are the current mainstay of treatment; however, chronic treatment with topical mid- to high-potency corticosteroids is contraindicated for the face, neck and intertriginous areas, and is associated with such adverse events as skin atrophy, hypopigmentation, striae, telangiectases, secondary infections, acne, skin hemorrhage, steroid rosacea, reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, and growth retardation in children [1, 2, 3, 4, 5, 6, 7, 8]. Also, severe or unresponsive disease may require short courses of systemic steroids, phototherapy (UVA, UVB) and/or a combination of psoralens and UVA (PUVA) in addition to topical corticosteroids, adding the risk of severe adverse events, rebound flaring after discontinuation, and cutaneous malignant lesions [1, 2, 4]. Alternating treatment regimens are often advised for patients undergoing long-term therapy with topical corticosteroids due to the risk of tachyphylaxis and the potential for decreased response to treatment over time.

Systemic immunosuppression (e.g., orally administered cyclosporine A) has also been used for recalcitrant disease; however, there are significant safety concerns [2].

Treatment options are limited and frequently provide suboptimal control, particularly for difficult to manage patients (e.g., those with severe or long-standing disease, extensive body surface area involvement, facial lesions, or young children).

A topical, nonsteroidal therapeutic agent which is effective monotherapy (even in severe disease), has a benign side effect profile (even with chronic use), can be used on all parts of the body including areas which are contra-indicated for the use of steroids, and which can be safely used in both adults and children (even young children) is highly desirable.

2.2 Tacrolimus Ointment

Tacrolimus, a macrolide immunomodulator, is marketed worldwide in both intravenous and oral formulations (Prograf®) for the prevention of organ rejection following allogeneic liver or kidney transplantation. Tacrolimus is known to block the early phase of T-cell activation by inhibiting the phosphatase activity of calcineurin [9, 10]. Calcineurin plays an essential role in the intracellular signal transduction pathway leading to the transcriptional activation of genes that encode cytokines which have been implicated in the pathogenesis of atopic dermatitis [11, 12, 13].

Tacrolimus ointment was developed specifically for the treatment of atopic dermatitis and represents the first in a new class of topical, nonsteroidal immunomodulators. In the United States, Fujisawa Healthcare, Inc. submitted the IND for tacrolimus ointment on December 15, 1994. Fujisawa Healthcare, Inc. met with the FDA at an end-of-Phase 2 meeting in October, 1998. During this meeting, the design of the pivotal clinical studies

supporting a proposed NDA were agreed upon along with the definition of the primary endpoint ≥ 90% improvement from baseline to the end of treatment based on the Physician's' Global Evaluation of Clinical Response; see also Section 7.1 and Section 8.1). The protocols for these studies were submitted to the IND in July of 1997. Following a pre-NDA meeting with the FDA in April, 1999, Fujisawa Healthcare, Inc. submitted the tacrolimus ointment NDA 50-777 to the FDA, Division of Dermatologic and Dental Drug Products on September 9, 1999.

As presented in NDA 50-777, tacrolimus ointment (0.03% and 0.1%) represents a safe and effective nonsteroidal topical therapy for the management of atopic dermatitis in both adult and pediatric patients and offers a number of potential clinical benefits. It is

- effective in the treatment of atopic dermatitis in adults and pediatric patients (2-15 years of age). It is effective as monotherapy even in the most difficult to manage cases (e.g., severe disease, extensive body surface area involvement, facial lesions, etc.).

- not associated with skin atrophy, striae, depigmentation or other skin disorders frequently associated with current therapy (e.g., topical corticosteroids) for atopic dermatitis, and can be safely administered to the face and neck as well as intertriginous areas.

- safe and effective even with prolonged daily use.

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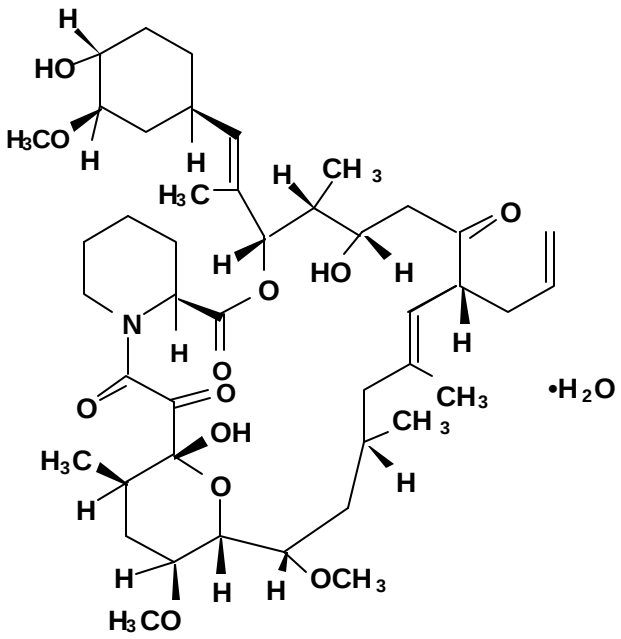
3 PHYSICAL AND CHEMICAL PROPERTIES

Tacrolimus, a macrolide produced by *Streptomyces tsukubaensis* and previously known as FK506, is the active ingredient of tacrolimus ointment. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**, 14*R**, 15*S**, 16*R**, 18*S**, 19*S**,26a*R**]]-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)–1-methylethenyl] - 14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c] [1,4] oxaazacylotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Figure 1: Chemical Structure of Tacrolimus



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12} \bullet H_2O$ and a formula weight of 822.05 daltons. Tacrolimus appears as white crystals or crystalline powder. It is soluble in many semi-polar solvents, but practically insoluble in water and hexane.

Tacrolimus ointment is an oleaginous ointment in which tacrolimus drug substance is dissolved in droplets of propylene carbonate, which are uniformly dispersed in the vehicle. Each gram of tacrolimus ointment contains either 0.03% or 0.1% tacrolimus (w/w) in a base of white petrolatum, mineral oil, propylene carbonate, white wax and paraffin.

Tacrolimus ointment is stable for 24 months when stored at 25°C (77°F) with excursions to 15°C-30°C (59°F-86°F).

4 NONCLINICAL PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOLOGY

Twenty-seven company-sponsored, nonclinical studies have been performed in support of the development of a topical formulation of tacrolimus; the data from these studies were included in NDA 50-777. Taken collectively, these studies, as well as reports in the literature, indicate that:

Pharmacology

- Tacrolimus, applied topically as an ointment, acts locally via multiple cell types (e.g., T-cells, mast cells, basophils, dendritic cells).

  In vitro, tacrolimus (a) inhibits the release of preformed mediators from skin mast cells and basophils, cells that may figure prominently in the early stages of atopic dermatitis; (b) reduces production of cytokine IL-13 by activated T-cells and mast cells; (c) influences the number of dendritic cells and percentage of Langerhans cells in epidermal cell suspensions from affected skin of atopic dermatitis patients, as well as downregulating high-affinity IgE receptor expression; and (d) decreases the stimulatory capacity of epidermal cells to their autologous lymphocytes [1-26].

  In animal models of allergic contact dermatitis, acute irritant dermatitis, and delayed-type hypersensitivity, tacrolimus ointment inhibits inflammatory skin reactions [27-32].

- In contrast to corticosteroid ointment, tacrolimus ointment does not induce skin atrophy.

  In mice [31], a reduction in normal ear thickness was observed with steroid ointments (0.1% alclometasone dipropionate, 0.12% betamethasone valerate) but not with tacrolimus ointment (0.1%, 0.3%, 1%). In a study in rats [33], skin weight, thickness, and histopathology (hematoxylin and eosin stain, proliferating cell nuclear antigen stain) in animals treated with tacrolimus ointment (0.3% applied daily for 3 weeks) were similar to those of the sham control. In contrast, corticosteroid ointments (0.05% clobetasol 17-propionate, 0.5% prednisolone, 0.05% clobetasone 17-butyrate and 0.12% betamethasone 17-valerate) were associated with decreased subcutaneous adipose tissue, thinning of the epidermis and dermis, and suppressed epidermal cell proliferation. In addition, decreases in the size of sebaceous glands and thinning of subcutaneous muscular layers were observed with clobetasol propionate.

Pharmacokinetics

- Tacrolimus is absorbed into the systemic circulation following topical administration, although the extent of absorption is low; the absorbed fraction varies with animal species.

- The fraction of the tacrolimus dose that reaches the systemic circulation is extensively distributed.

- Tacrolimus does not accumulate in tissues following repeated topical application.

Toxicology

- A single application of tacrolimus ointment, with or without occlusion, to intact or abraded skin does not produce skin abnormalities.

- Repeated daily application of tacrolimus ointment in studies conducted up to 1 year to assess topical toxicity is associated with mild to moderate dermal irritation and microscopic findings of acanthosis, hyperkeratosis, and superficial inflammation; these findings have also been observed with vehicle.

- Tacrolimus ointment does not induce contact hypersensitivity, phototoxicity, photosensitization, or depigmentation.

It was established early in the development of Prograf (tacrolimus [FK506] capsules, tacrolimus injection [for intravenous infusion only]) that tacrolimus is not carcinogenic [see Prograf Package Insert, "*Carcinogenesis, Mutagenesis and Impairment of Fertility*"]. As part of the development of tacrolimus ointment, a 24-month study was conducted to evaluate dermal oncogenicity following repeated application of 0.03% to 3% tacrolimus ointment (1.6 to 157.9 mg/kg per day) to $B6C3F_1$ mice. In this 24-month study, application of tacrolimus ointment was not associated with skin tumor formation; however, in the 0.1% tacrolimus group (5.3 mg/kg per day), the incidence of lymphoma was significantly increased (Peto analysis $p<0.0001$) compared with study controls. Whether these lymphoma findings have relevance to the development of lymphoproliferative disorders in patients must be considered in light of several factors:

- These animals had a much higher systemic exposure to tacrolimus than would be expected in atopic dermatitis patients. Rodents are known to have a much more permeable skin than man [34]. In this study, this higher basal permeability was further increased since these animals were repeatedly clipped damaging the skin barrier (stratum corneum). High cutaneous absorption resulted in higher systemic exposure in this study than that previously observed when rodents were fed equivalent doses of tacrolimus (in dietary studies conducted during the development of Prograf) [Company Document 000602].

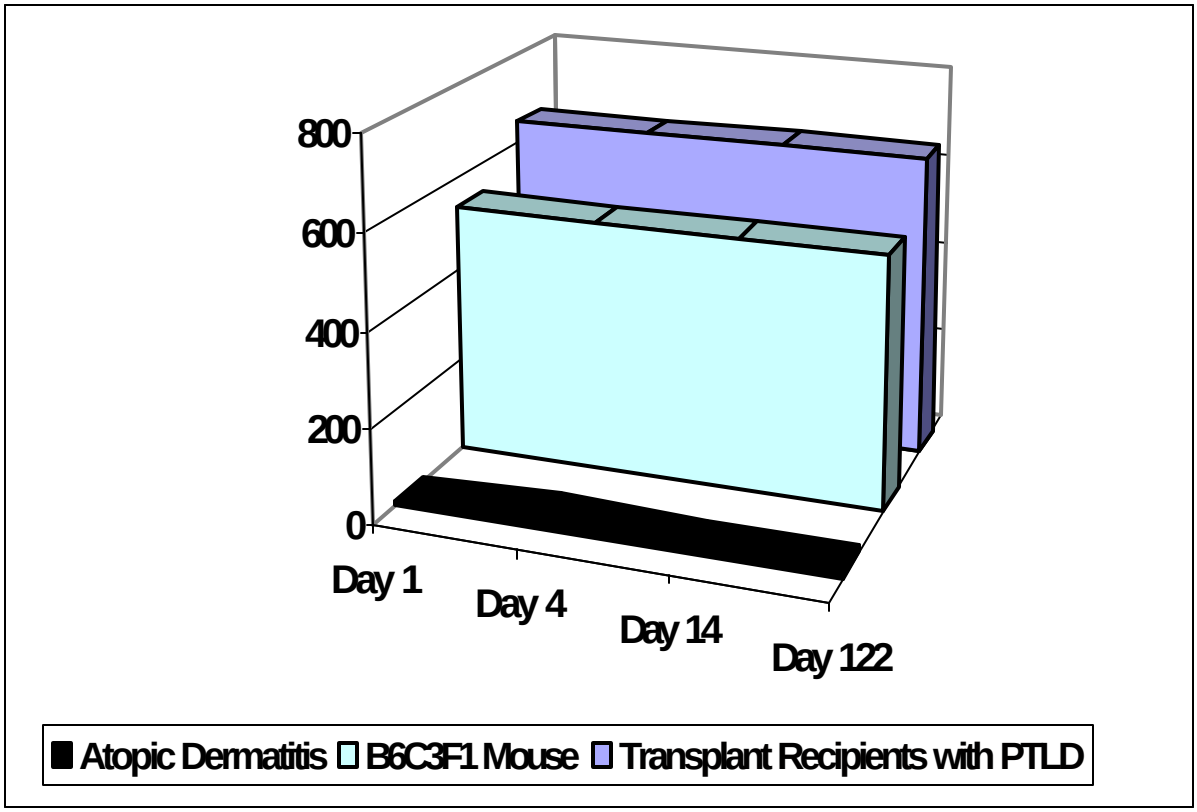
  To give this systemic exposure a clinical perspective, a hypothetical "worst case" atopic dermatitis exposure scenario has been constructed for comparative purposes based on observed pharmacokinetic profiles in atopic dermatitis patients applying 0.1% tacrolimus ointment over an extensive portion of affected body surface area (mean BSA affected: 53%; see also Section 5.3.4). This hypothetical "worst case" scenario overestimates actual exposure since it assumes that quantifiable blood concentrations are observed for prolonged periods and the absorption remains constant despite lesion healing and a rapidly decreasing proportion of affected body surface area – all these assumptions are contrary to clinical evidence. As presented in NDA 50-777, quantifiable blood concentrations are isolated events generally observed early in treatment and at a single sampling time. Affected body surface area decreases rapidly during treatment with tacrolimus ointment, generally within 1 week. Using this scenario, exposure to tacrolimus for atopic dermatitis patients was determined to be **46-fold lower** than that of mice who developed lymphoma in the oncogenicity study () [Company Document 000602].

- Lymphomas observed in carcinogenicity/oncogenicity models routinely used in drug development are not equivalent to human lymphoproliferative disorders/lymphomas associated with intense immunosuppressive therapy. Human lymphoproliferative disorders/lymphomas (PTLD) differ both from counterpart lymphomas observed in the general population (e.g., with respect to extranodal involvement, location of lesions, and patient management [35]) and from lymphomas observed in lower animals (e.g., PTLD is associated with Epstein-Barr viral infection (35, 36); human Epstein-Barr viral infection is not naturally observed in animals such as rodents).

  The development of PTLD has been described for transplant recipients on immunosuppressive regimens which include such agents as cyclosporine, corticosteroids, azathioprine, OKT3 and Prograf [35, 36, 37; Prograf package insert]. However, the immunomodulator regimens used to treat atopic dermatitis are vastly different from those designed to maintain transplant patients in a chronically immunosuppressed state. Again, using the hypothetical "worst case" scenario and blood concentration data collected in clinical/pharmacokinetic studies, exposure to tacrolimus for atopic dermatitis patients applying tacrolimus ointment was determined to be **56-fold lower** compared with transplant patients who developed PTLD during Prograf therapy () [Company Document 000602].

Of the 2,847 patients included in NDA 50-777, 676 applied 0.1% tacrolimus ointment for at least a year. In addition, 183 of the 2,847 have applied 0.1% tacrolimus ointment during at least a year's participation in an extension study (Study 97-0-038). There has been no clinical evidence of systemic immunosuppression nor lymphomas related to tacrolimus ointment use in the tacrolimus ointment development program.

Figure 2: Relative Tacrolimus Exposure in Transplant Recipients and Mouse Oncogenicity Model Compared With Atopic Dermatitis Patients



Based on theoretical median $AUC_{0\text{-}onset}$ (ng•hr/mL) for 15 transplant recipients receiving Prograf in clinical trials who developed PTLD and had blood concentration data available and their median time to onset of PTLD of 122 days [divide the theoretical median $AUC_{0\text{-}onset}$ by 122 to plot an estimated median value per day]. Based on mean daily AUC in 0.1% tacrolimus ointment group in 24-month mouse oncogenicity study. Based on mean $AUC_{0\text{-}12}$ data from worst case pharmacokinetic study in atopic dermatitis patients. Created assuming worst case for atopic dermatitis patient exposure to tacrolimus following topical application (i.e., in group with highest mean $AUC_{0\text{-}12}$ (on Day 4), Day 1 daily value was maintained for 3 days, Day 4 daily value was maintained for 10 days and Day 14 daily value was maintained for the remaining 109 days [period equivalent to median time to onset of PTLD in transplant recipients].

This is an overestimation of exposure in atopic dermatitis patients since clinical data support that quantifiable blood concentrations are NOT observed for prolonged periods, absorption decreases concurrently with lesion healing and that affected body surface area decreases within 1 week of the start of treatment with tacrolimus ointment.

In a 52-week photocarcinogenicity study, albino hairless Crl:SKH1-*hr*BR mice (36/sex/group) were treated with tacrolimus ointment (0.03%, 0.1%, 0.3%, and 1%) or vehicle ointment and exposed to simulated solar ultraviolet radiation (low and high UVR) in a model designed to produce skin tumors in all animals. When the combined male and female tumor data were evaluated, the indication was that the 1.0% concentration enhanced the development of UVR-induced skin tumors as compared with vehicle-treated mice; however, enhancement was not evident at the 0.03%, 0.1% (the clinically relevant concentrations) or 0.3% concentrations. When tumor data were evaluated based on sex, administration of the 0.03% concentration had no influence on the development of UVR-induced skin tumors in either male or female mice, as compared with vehicle-treated mice. In male mice, administration of the 0.1%, 0.3%, and 1.0% concentrations shortened the time to skin tumor production as compared to vehicle-treated males.

The relevance of these findings to humans is not known. When asked to comment on the results of this study, Drs. PD Forbes and F Urbach, experts in the area of photobiology and developers of the standard photocarcinogenesis hairless mouse model in current use, stated that as a risk assessment tool for humans this model is undeveloped [Company Document No. 000821, August 21, 2000]. Photocarcinogenesis studies have not yet provided a basis for estimating risks to man from increased exposure to those chemicals or pharmaceutical agents that have been shown to enhance photocarcinogenesis in mice. Tacrolimus ointment is not photoreactive. The primary effect observed in the hairless mouse photocarcinogenesis model is due to vehicle; vehicle effects are known and well-documented. The contribution of tacrolimus (drug substance) was only modest above that of vehicle. Enhancement was found for 1 and 2 mm tumors but not for 4 mm tumors suggesting that tacrolimus ointment had not produced a measurable difference in tumor growth rates. The limited reduction of tumor latent period, at exaggerated dosing levels

far more intensive in terms of drug delivery and duration of therapy than for intended human use, supported little or no systemic influence. Dr. Forbes and Urbach stated that the enhanced response should be noted but not considered a predictor of a clinically detectable carcinogenic potential in man. Regulatory management of photocarcinogenesis findings in this model for other compounds (e.g., Tazorac® 0.05%, 0.1% [tazarotene] topical gel approved 1997; Lac-Hydrin ® 12% [ammonium lactate] cream approved 1996; Renova® 0.05% [tretinoin] emollient cream approved 1995) has been limited to a cautionary statement in labeling indicating that patients under treatment should minimize concomitant exposure to sunlight or other sources of UVR. Similar language is contained in the proposed draft package insert for tacrolimus ointment.

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Package Insert

Prograf [package insert]. Deerfield, IL: Fujisawa Healthcare, Inc.; October, 1998.

5 CLINICAL PHARMACOKINETICS AND PHARMACOLOGY

A total of 11 clinical pharmacology studies were performed as part of the development of tacrolimus ointment (Appendix I) and the results reported in detail in NDA 50-777. Of these 11 studies, 6 patch test studies and 1 study evaluating the atrophogenic potential of tacrolimus ointment, as well as tacrolimus blood concentration data from two pharmacokinetic studies in atopic dermatitis patients, are summarized in this briefing document. The results of a pharmacokinetic study in healthy volunteers and an immunohistological study can be found in NDA 50-777.

5.1 Patch Test Studies

Six of the 11 studies were patch test studies evaluating tacrolimus ointment at concentrations ranging from 0.03%-0.3% in healthy volunteers (Studies 94-0-004, 94-0-005, 94-0-006, 94-0-007, 95-0-011 and 97-0-026). The studies compared tacrolimus ointment with vehicle, other marketed formulations used to treat inflammatory dermatoses (calcipotriene, hydrocortisone, and betamethasone valerate ointments) or with another control substance (sodium lauryl sulfate). Ointments (0.12 g) were applied to 3 cm^2 areas of intact skin on the back of each healthy volunteer. Irritation was graded by the investigator using a 5-point scale (0 = No sign of irritation to 4 = erythema with edema and blistering). Taken collectively, the results of these studies demonstrated that tacrolimus, relative to other products, is not inherently irritating, sensitizing, phototoxic, or photoallergenic when applied as ointment to intact skin.

5.2 Pharmacology: Evaluation of Atrophogenic Potential

In pharmacodynamic Study FG-06-17 [1], the effects of 0.1% and 0.3% tacrolimus ointment, vehicle, and 0.1% betamethasone valerate ointment (a known atrophogenic corticosteroid) on collagen synthesis were evaluated in unaffected skin of atopic dermatitis patients (n=14) and in healthy volunteers (n=12), using a patch test-like design. Two applications of tacrolimus ointment, vehicle or betamethasone valerate ointment were performed during a 7-day period to separate 4X4 cm abdominal squares. Exposure to 0.1% or 0.3% tacrolimus ointment under occlusion over 7 days did not result in reduced collagen synthesis or skin thickness relative to vehicle control, suggesting that tacrolimus ointment does not produce skin atrophy. In contrast, similar exposure to the steroid ointment statistically significantly reduced both parameters relative to tacrolimus ointment and vehicle.

These findings are consistent with the results of an open-label study conducted in Japan (Study FJ-111) evaluating the 0.1% tacrolimus ointment concentration. One of the objectives of this study was to collect data on skin disorders. In this study, 53% (300/568) of atopic dermatitis patients entered the study with skin disorders associated with previous therapy (e.g., skin atrophy, capillary vasodilatation, rosacea-like dermatitis/perioral dermatitis-like findings). By the end of 1 year on study, the incidence of each of these disorders was reduced by approximately half and the severity of these symptoms was substantially ameliorated for most patients.

5.3 Pharmacokinetics

The analysis of tacrolimus blood concentration data from three pharmacokinetic studies (healthy volunteer Study FG-06-04; atopic dermatitis patient Studies 94-0-008 and FJ-106) included in NDA 50-777 indicates minimal absorption into the systemic circulation following single or repeated application to intact or affected skin. Tacrolimus blood concentrations obtained in four of the five clinical studies which formed the core of NDA 50-777 were also consistent with minimal absorption through diseased skin. Patients with quantifiable levels did not experience these concentrations for prolonged periods but generally only at a single sampling time and in one blood sample. There is no evidence for systemic accumulation. [See Sections 7.1 and 7.2 for a description of these core studies; note that blood was not collected for tacrolimus concentration determination in the fifth core study of the NDA, a long-term pediatric study].

Blood concentration results from the two pharmacokinetic studies in patients, as well as from the four core studies, are presented in this briefing document. Also presented are the results from two recently conducted European pharmacokinetic studies evaluating the effect on tacrolimus blood concentrations of applying 0.1% tacrolimus ointment to increasing affected body surface area and the results of a population pharmacokinetic analysis of blood concentration data from six US clinical trials.

5.3.1 Tacrolimus Blood Concentration: Patient Study 94-0-008

In pharmacokinetic Study 94-0-008 [2] in 31 adult and 8 pediatric atopic dermatitis patients, tacrolimus was minimally absorbed into the systemic circulation following single or repeated application for 8 days of 0.3% tacrolimus ointment to affected skin (Note: this concentration is 3 to 10 times that of the proposed commercial product). Although a direct determination of bioavailability in humans has not been made for tacrolimus ointment, a comparison of AUC_{0-24} data from this study with historical data after oral and intravenous administration of Prograf (tacrolimus capsules, tacrolimus injection) to healthy volunteers indicated an absolute bioavailability of ≤0.5% (Table 4).

Table 4: Estimated Absolute and Relative Bioavailability (%) of Topically Administered Tacrolimus in Study 94-0-008

Method of Administration	Dose (mg)	Mean AUC_{0-24} (ng·hr/mL)	Absolute $\frac{AUC_{Topical}/dose}{AUC_{IV}/dose} \times 100$	Relative $\frac{AUC_{Topical}/dose}{AUC_{Oral}/dose} \times 100$
Intravenous (IV)	2	346 (173)		
Oral (PO)	5	163 (33)		
Topical (day 1)	45†	42.5 (0.9)	0.5	2.7
Topical (day 8)		27.3 (0.6)	0.3	1.8

( ): AUC normalized to 1 mg
†Highest amount applied in the study; patient with the highest AUC.

This level of systemic exposure diminished (as indicated by a comparison of Day 1 and Day 8 AUCs) with repeated application, concurrent with improvement of skin condition. There was no evidence of systemic accumulation (Figure 3).

In Study 94-0-008, only one adult patient (Patient No. 85021 treating 5,000 cm^2) had a blood concentration ≥5 ng/mL (9.42 ng/mL at 6 hours postapplication on Day 1); the tacrolimus blood concentration for this patient decreased over time and was 0.45 ng/mL on Day 11. The highest individual tacrolimus blood concentration in a pediatric patient

was 3.28 ng/mL (Patient No. 85025) 4 hours postapplication on Day 1; the blood concentration for this patient was 0.54 ng/mL at 8 hours postapplication on Day 1, 0.08 ng/mL 1 hour after application on Day 8, and below 0.05 ng/mL (below LOQ) when sampled at 4 and 8 hours postapplication on Day 8 and on Days 9 and 11.

5.3.2 Tacrolimus Blood Concentration: Patient Study FJ-106

Tacrolimus blood concentrations following single and repeated topical application of tacrolimus ointment (0.1% or 0.3%) was investigated in 21 adult atopic dermatitis patients in Study FJ-106. The observed blood concentration-time profile was similar for equivalent doses to that observed in US Study 94-0-008. One patient in the single dosing group and one patient in the repeated dosing group, both with severe disease applying 10 grams of 0.1% tacrolimus ointment per application, had an individual concentration ≥5 ng/mL; these concentrations were transient.

5.3.3 Tacrolimus Blood Concentration: Core Studies

In three US Phase 3 studies (12-week, double-blind, Studies 97-0-035, 97-0-036, and 97-0-037), blood was collected from patients at Day 1, Week 1, Week 3, and Week 12/end of treatment in order to determine whole blood tacrolimus concentrations using a validated ELISA method (limit of quantitation, LOQ, 0.5 ng/mL). In the European Phase 3 adult safety study (up to 1 year, 0.1% tacrolimus ointment; Study FG-06-12), blood was collected at Day 1, Week 1, Week 2, Month 1, Month 3 and the last visit; blood was analyzed using a validated high performance liquid chromatography method with repeated mass spectrometry (HPLC-MSMS; LOQ 0.025 ng/mL).

In these studies, tacrolimus blood concentrations were consistent with minimal absorption of drug through diseased skin (Table 5 and Table 6).

The highest individual tacrolimus blood concentration was ≥ 5 ng/mL in 0.5% (4/754) of patients in these studies (Table 5); these few patients did not experience this concentration for a prolonged period but only at a single sampling time and in one blood sample (a total of 4 samples out of 2679 samples collected).

Mean and median blood concentrations were below 0.5 ng/mL at all time points in patients applying either the 0.03% or the 0.1% tacrolimus ointment concentration (Table 6). Quantifiable tacrolimus blood concentrations following topical application were isolated events, generally observed early in treatment.

These data also support no systemic accumulation.

The adverse event profile of patients with a quantifiable tacrolimus blood concentration at any time during the study was generally consistent with that of patients without quantifiable levels. For example, when the raw incidence rates for adverse events which showed a statistically significant difference in incidence between either tacrolimus ointment concentration and vehicle in the three US double-blind studies (Studies 97-0-035, 97-0-036, 97-0-037) were compared between patients who had blood collected for tacrolimus determination and had a quantifiable blood concentration (≥0.5 ng/mL) anytime during treatment (n=146) and those that did not (n=297), there was no statistically significant difference in the incidence of nonapplication site adverse events.

Only two application site events, hyperesthesia and folliculitis, showed a statistically significant difference in incidence.

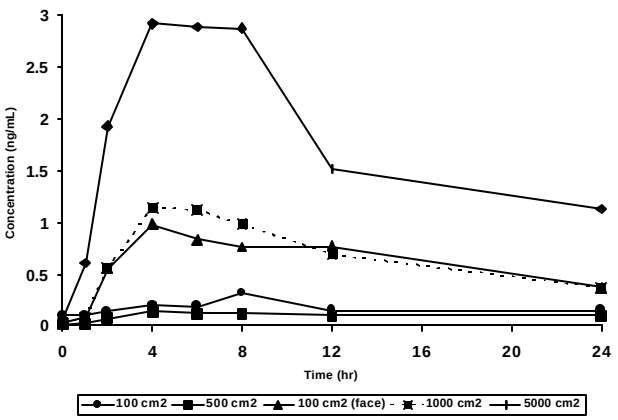
Hyperesthesia (*sensitive skin, skin sensitive to temperature change, etc.*) had a 8.9% incidence in patients with a quantifiable level and 1.7% in those with no quantifiable levels (Fisher's exact test, p=0.001). All patients with hyperesthesia experienced it as an application site event, with one of these patients also experiencing it in a nonapplication site. Hyperesthesia is a topical effect that may be related to the local action of tacrolimus ointment.

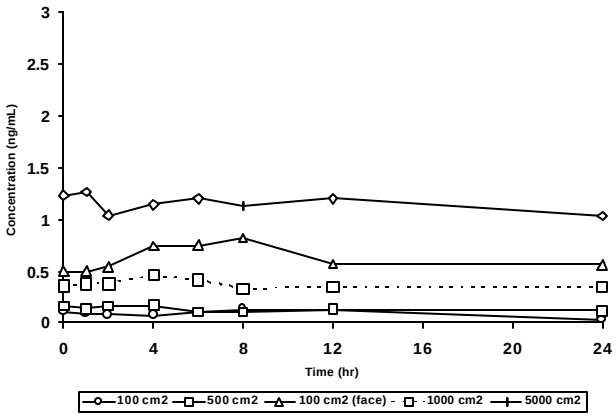
Folliculitis had a 8.9% incidence in patients with a quantifiable level and 2.7% in those with no quantifiable levels (Fisher's exact test, p=0.007). However, when the percentage of affected body surface area at baseline was adjusted in a logistic regression model, there was no statistically significant difference in the incidence of folliculitis (p=0.125).

Figure 3: Mean Tacrolimus Blood Concentration-Time Profiles In Adult and Pediatric Atopic Dermatitis Patients (Study 94-0-008)

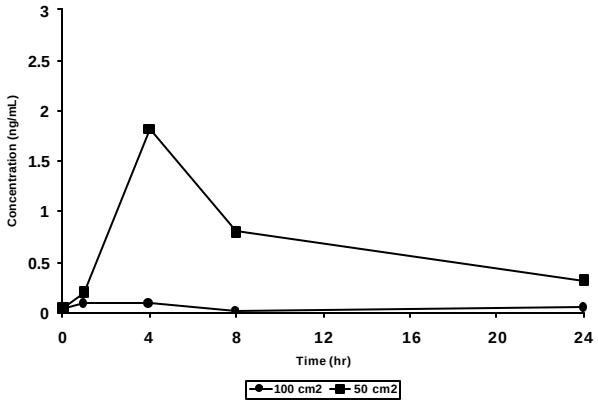
Day 1 *Day 8*

Adult Patients (n=31)





Pediatric Patients (n=8)



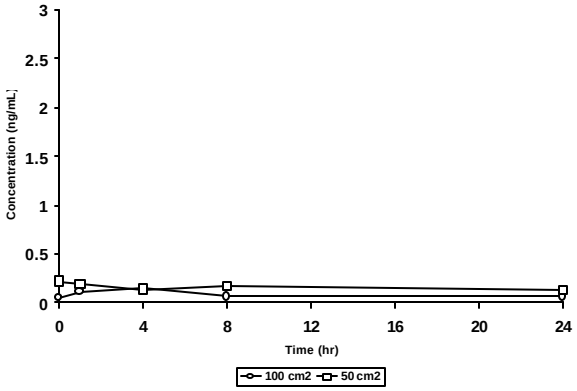


Table 5: Distribution of Highest Individual Tacrolimus Blood Concentrations in Patients in Core Studies

Study	Ointment Concentration	n*	No. of Patients With The Indicated Highest Individual Tacrolimus Blood Concentration (ng/mL)					Maximum Concentration (ng/mL)
			<0.5	0.5 – <1	1 - <2	2 - <5	³5	
97-0-035‡#	0.03%	98	74	15	5	3	1	5.82
	0.1%	91	55	14	18	4	0	3.96
97-0-036‡	0.03%	97	63	25	6	2	1	8.13
	0.1%	102	59	29	6	7	1	5.30
97-0-037‡ (pediatric)	0.03%	25	22	2	1	0	0	1.19
	0.1%	30	24	4	1	1	0	2.28
FG-06-12◊ Long-term Safety	0.1%	311	155	86	52	17	1	5.75
Total		**754**	**452 (60.0%)**	**175 (23.2%)**	**89 (11.8%)**	**34 (4.5%)**	**4 (0.5%)**	

*N: Patients who were treated and had tacrolimus blood concentrations measured.

LOQ: Limit of quantitation; ‡ ELISA, LOQ 0.5 ng/mL; ◊ HPLC-MSMS, LOQ 0.025 ng/mL

#One 15-year-old was enrolled in this adult study. This patient did not have quantifiable tacrolimus blood concentrations. Source: NDA 50-777 (Section 6).

Table 6: Tacrolimus Blood Concentration (ng/mL) – Summary Over Time of Mean ± Standard Deviation, Median and Range in 12-Week Double-Blind Studies and Adult Long-Term Safety Study

6A. Pediatric Study 97-0-037

Study Week	Variable	Concentration of Tacrolimus Ointment	
		0.03%	**0.1%**
All Patients (2-15 Years of Age)		**n=25**	**n=30**
1	n	21	26
	Mean ± SD	0.08 ± 0.28	0.16 ± 0.35
	Median	0.00	0.00
	Range	0.00 - 1.19	0.00 -1.31
3	n	20	26
	Mean ± SD	0.04 ± 0.16	0.20 ± 0.51
	Median	0.00	0.00
	Range	0.00 - 0.70	0.00 - 2.28
12	n	15	18
	Mean ± SD	0.04 ± 0.16	0.10 ± 0.42
	Median	0.00	0.00
	Range	0.00 - 0.64	0.00 - 1.79
Patients 2-6 Years of Age		n=16	n=17
1	n	13	15
	Mean ± SD	0.13 ± 0.35	0.28 ± 0.43
	Median	0.00	0.00
	Range	0.00 - 1.19	0.00 - 1.31
3	n	12	13
	Mean ± SD	0.06 ± 0.20	0.40 ± 0.67
	Median	0.00	0.00
	Range	0.00 - 0.70	0.00 - 2.28
12	n	11	10
	Mean ± SD	0.06 ± 0.19	0.18 ± 0.57
	Median	0.00	0.00
	Range	0.00 - 0.64	0.00 - 1.79

Patient population: all randomized patients who received at least one dose of study drug and had blood collected for blood concentration determination. Tacrolimus blood concentrations were determined using a validated ELISA method with a lower limit of quantitation of 0.5 ng/mL. Values below 0.5 ng/mL were considered to be zero. No patient 7-15 years of age had a measurable tacrolimus blood concentration.
Source: NDA 50-777, Study Report R98-0214-506-C3-E.

6B. Adult Study 97-0-035

Study Week	Variable	Concentration of Tacrolimus Ointment	
		0.03%	**0.1%**
Total Number of Patients		98	91
1	n	91	86
	Mean ± SD	0.215 ± 0.77	0.335 ± 0.74
	Median	0.00	0.00
	Range	0.00 - 5.82	0.00 - 3.96
3	n	86	75
	Mean ± SD	0.147 ± 0.42	0.246 ± 0.52
	Median	0.00	0.00
	Range	0.00 - 2.47	0.00 - 2.00
12	n	63	59
	Mean ± SD	0.174 ± 0.55	0.157 ± 0.37
	Median	0.00	0.00
	Range	0.00 - 2.47	0.00 - 1.40

Patient population: all randomized patients who received at least one dose of study drug and had blood collected during treatment for tacrolimus concentration determination. Tacrolimus blood concentrations were determined using a validated ELISA method with a lower limit of quantitation of 0.5 ng/mL. Values below 0.5 ng/mL were considered to be zero.
Source: NDA 50-777, Study Report L1999000006

6C. Adult Study 97-0-036

Study Week	Variable	Concentration of Tacrolimus Ointment	
		0.03%	**0.1%**
Total Number of Patients		97	102
1	n	85	90
	Mean ± SD	0.263 ± 1.02	0.330 ± 0.73
	Median	0.00	0.00
	Range	0.00 - 8.13	0.00 – 3.85
3	n	68	79
	Mean ± SD	0.110 ± 0.30	0.363 ± 0.79
	Median	0.00	0.00
	Range	0.00 - 1.46	0.00 – 5.30
12	n	48	60
	Mean ± SD	0.264 ± 0.45	0.238 ± 0.60
	Median	0.00	0.00
	Range	0.00 - 1.83	0.00 - 2.82

Patient population: all randomized patients who received at least one dose of study drug and had blood collected during treatment for tacrolimus concentration determination. Tacrolimus blood concentrations were determined using a validated ELISA method with a lower limit of quantitation of 0.5 ng/mL. Values below 0.5 ng/mL were considered to be zero.
Source: NDA 50-777, Study Report L1999000008.

6D. Adult Long-Term Study FG-06-12

Visit	n	Mean ± SD	Median (min-max)
Day 1	288	0.04±0.14	0 (0-1.39)
Week 1	282	0.47±0.57	0.32 (0-3.88)
Week 2	273	0.48±0.52	0.30 (0-3.20)
Month 1	274	0.39±0.41	0.26 (0-2.50)
Month 3	251	0.31±0.41	0.18 (0-2.83)
Month 6	219	0.34±0.63	0.14 (0-5.75†)
Month 12	62	0.28±0.46	0.13 (0-2.19)

Patient population: all enrolled patients who received at least one dose of 0.1% tacrolimus ointment and had blood collected during treatment for tacrolimus concentration determination.
Tacrolimus blood concentrations were determined using a validated HPLC-MSMS method with a lower limit of quantitation of 0.025 ng/mL.
Based on the highest individual concentration of each patient during the study.
Values below the limit of reliable quantification (0.025 ng/mL) were set to 0.
† At the time this blood sample was collected, Patient No.00004408 was experiencing an atopic dermatitis "flare".
Source: NDA 50-777, Study Report FG98-506-07

5.3.4 Tacrolimus Blood Concentration: Treatment of Extensive Body Surface Area in Two European Studies

Two studies, one in adults (FG-06-22) and one in children (6-12 years of age)(FG-06-23; ongoing) with moderate to severe atopic dermatitis were recently conducted in Europe to evaluate the pharmacokinetics of tacrolimus following topical application of 0.1% ointment to various sized treatment areas. Pharmacokinetic parameters for patients in the groups treating the largest application area in these two studies are summarized in Table 7.

AUC did increase with increasing application area; however, even with up to 83% of the body surface area treated, the extent of systemic exposure was minimal following topical

application of tacrolimus ointment. There was no evidence of systemic accumulation with repeated application.

Table 7: Pharmacokinetic Parameters

	Mean % BSA Treated	Parameter	Day 1	Day 4	Day 14
Adult Study	53 [36-60]	**C_{max} (ng/mL) mean±sd range**	0.66 ± 0.85 n=9 0.06-2.83	0.96 ± 0.80 n=9 0.12-2.70	0.65 ± 0.38 n=9 0.06-1.40
		AUC_{0-12} (ng·hr/mL) mean±sd range	4.8 ± 6.3 n=9 0.3-20.8	10.2 ± 9.2 n=9 1.1-31.0	5.4 ± 2.8 n=9 0.7-10.1
Pediatric Study	61 [49-72]	**C_{max} (ng/mL) mean±sd range**	0.70 ± 0.98 n=2 0-1.39	0.06-0.60† n=2	0.33 ± 0.38 n=2 0.06- 0.60
		AUC_{0-24} (ng·hr/mL) mean±sd range	10.6 ± 15.0 n=2 0-21.1		4.7 ± 5.3 n=2 0.93-8.42
	63 [52-83]	**C_{max} (ng/mL) mean±sd range**	0.62 ± 0.48 n=7 0.026-1.51	0.12-1.02† n=4	0.21 ± 0.18 n=7 0.05-0.59
		AUC_{0-24} (ng·hr/mL) mean±sd range	8.9 ± 8.8 n=7 0.08-26.5		4.1 ± 3.6 n=7 0.69-11.4

Treatment: 0.1% tacrolimus ointment.
Assay: LCMSMS (LOQ=0.025 ng/mL); values below LOQ were considered to be 0.
†Highest and lowest predose (trough) concentration in ng/mL.
Adult Study: Blood was collected predose and 2, 4, 6, 8, 10, 12 and 24 hours after first application on Days 1 and 4; and predose, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 and 168 hours after the only application on Day 14. Pediatric Study: Blood was collected predose and 2, 4, 8 and 24 hours after application on days 1 and 14 with an additional 96 hour sample on Day 14 and one sample before application on Day 4.

5.3.5 Population Pharmacokinetics

In contrast to classic pharmacokinetics in which a series of samples are obtained from a few individuals in order to construct a small number of individual profiles which can be averaged together, population pharmacokinetics uses few samples from a larger number of patients in order to determine a central tendency for a population. Population pharmacokinetics is a means of supporting/supplementing the observations made in the classical manner and expanding the pharmacokinetic database of a drug development program [3].

Population pharmacokinetic analyses (NONMEM) were performed using data from 462 patients from whom blood was collected over a treatment period of 3 to 12 weeks in six US Phase 2 and 3 trials in the tacrolimus ointment development program (95-0-003, 95-0-009, 95-0-013, 97-0-035, 97-0-036 and 97-0-037). In these studies, the average percent body surface area affected was 43%.

Based on data from these 462 patients, the average steady state tacrolimus blood concentration was 0.25 ng/mL.

When age group (2 to 6 years of age, greater than or equal to 7 years of age) was incorporated as a covariate into the model, it was not a predictor of exposure (i.e., the results were comparable to those of the entire population). Therefore, the results/conclusions based on data from all patients can be applied to patients as young as 2 years of age.

Literature Cited

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6 OVERVIEW OF THE TACROLIMUS OINTMENT CLINICAL DEVELOPMENT PROGRAM: GLOBAL EXPERIENCE

The tacrolimus ointment development program included a total of 3,446 patients/healthy volunteers who applied at least one dose of tacrolimus ointment and were included in the safety analyses in 28 studies (8 Phase 1 and 20 Phase 2 or 3 studies) conducted in the United States, Europe, or Japan [Appendix II]. Of these individuals, 2,847 patients with atopic dermatitis applied tacrolimus ointment at concentrations ranging from 0.03% to 0.5% in Phase 2 or 3 clinical studies and were evaluable for safety. These included 1410 (50%) male patients and 1437 (50%) female patients ranging from 2 to 81 years of age (mean ± standard deviation, 24.8 ± 13.7 years). A total of 1202 (42%) patients were white, 317 (11%) were African American, and 1291 (45%) were Asian. A total of 665 (23%) patients were less than 16 years of age, with 287 (10%) being young children (2 to 6 years of age).

The number of patients/subjects is summarized by study in Table 8.

Table 8: Patient/Subject Accountability: Safety Evaluable Population

Protocol Number	Phase	Number of Tacrolimus Ointment-Treated Patients (P)/Healthy Volunteers (HV)
94-0-004†	1	30 HV
94-0-005†	1	12 HV
94-0-006†	1	30 HV
94-0-007†	1	30 HV
95-0-011†	1	229 HV
97-0-026†	1	228 HV
FG-06-04‡	1	14 HV
FG-06-17‡	2*	26 [12 HV, 14 P]
Total - Eight Phase 1 Studies		**599 [585 HV and 14 P]**

Table continued on next page

(Table 8 continued)

Protocol Number	Phase	Number of Tacrolimus Ointment-Treated Patients		
		0.03%	0.1%	³0.3%
94-0-008†	2	0	0	39
FJ-106§	2	0	17	4
97-0-030†	2	0	12	0
95-0-003†	2	43	49	44
FG-06-01‡	2	54	54	51
95-0-009†	2	12	13	0
95-0-013†	2	7	6	7
FJ-103§	2	17	18	12
FJ-104§	2	48	50	51
FJ-105§	2	0	49	94
FJ-107§	2	70	69	0
Total - Eleven Phase 2 Studies; 890 Patients		**251**	**337**	**302**
97-0-037†	3	117	118	0
97-0-035†	3	103	99	0
97-0-036†	3	108	110	0
FJ-108§	3	0	88	0
FJ-109§	3	0	75	0
96-0-025†	3	0	255	0
FG-06-12‡	3	0	316	0
FJ-111§	3	0	568	0
FJ-110§	3	0	62§§	0
Total - Nine Phase 3 Studies; 1957 Patients		**328**	**1629**	**0**
Total Phase 2 and 3; 2847 Patients		**579**	**1966**	**302**
Overall Total Phase 1, 2, and 3		**3446 Patients/Healthy Volunteers**		

Safety evaluable: included in the safety analyses. HV: healthy volunteers. P: patients.
† United States. ‡ Europe. § Japan.
* Included as a Phase 1 study in global experience analysis in view of its *patch test-like* study design.
§§ Study FJ-110 is an extension study of FJ-109; patients were enrolled in the 0.1% tacrolimus ointment treatment group Study in FJ-109. These patients are only counted once in the total for Phase 3 studies, Phase 2 and 3 studies, and in the overall total.
Source: NDA 50-777 (Statistical Appendices 8.4.13.10.1.5 and 8.4.13.10.1.6)

A total of 585 healthy volunteers and 14 patients received up to 18 applications of study drug in six patch test studies, a pharmacokinetic study (Study FG-06-04), and a pharmacodynamic study (Study FG-06-17). Drug exposure in the remaining 20 clinical studies is summarized in Table 9.

Table 9: Exposure In Phase 2 And 3 Studies: Safety Evaluable Population

Cumulative Days On Treatment	Concentration of Tacrolimus Ointment		
	0.03% n = 579	**0.1%** n = 1966	**³0.3%** n = 302
	Number of Safety Evaluable Patients With Indicated Treatment Days		
≥1 Day	579	1966	302
≥1 Week	563	1922	290
≥3 Weeks	471	1775	169
≥12 Weeks	220	1306	0
≥6 Months	0	971	0
≥12 Months	0	676	0

Safety evaluable: included in the safety analyses in 20 clinical Phase 2 or 3 studies.
Source: NDA 50-777 (Statistical Appendix 8.4.13.10.1.1).

[Note on data not included in the above table or in this briefing document: Preliminary safety data on 785 of these patients enrolled in extension Study 97-0-038 (381 pediatric patients 2-15 years of age and 404 adults ≥ 16 years of age), as well as preliminary safety data from two recently completed 3-week European studies (FG-06-18 and FG-06-19, 570 adult and 560 pediatric patients) were submitted as part of the 120-day safety update for NDA 50-777. The median total exposure to tacrolimus ointment for patients in the US extension study (treatment days in initial study plus study days in 97-0-038) was 365 days, with 56% of these patients exposed for ≥12 months and 16% exposed for ≥ 18 months. The safety information from these studies is consistent with that presented in the original submission.]

Demographic, exposure and adverse event data were similarly structured/coded for the studies which comprise the global safety experience with tacrolimus ointment. The adverse event profile for the 2847 patients in the 20 clinical Phase 2 or 3 studies who applied tacrolimus ointment at concentrations ranging from 0.03% to 0.5% was consistent with that observed in the three 12-week, double-blind, Phase 3 studies and two long-term, Phase 3 studies which form the core of NDA 50-777 (see Section 9).

7 CORE STUDIES

It was agreed at the end-of-Phase 2 meeting between Fujisawa Healthcare, Inc. and the FDA (October 28, 1996) that five core studies would be adequate to support the indication:

- *12-Week, Double-Blind Studies:* Three multicenter, randomized, vehicle-controlled 12-week studies conducted in the United States; one in pediatric patients (Study 97-0-037) and two in adult patients (Studies 97-0-035 and 97-0-036) evaluating the 0.03% and 0.1% tacrolimus ointment concentrations.
- *Long-Term Safety Studies:* Two multicenter, open-label, single concentration (0.1% tacrolimus ointment), long-term (up to 12 months) studies; one conducted in the United States in pediatric patients (Study 96-0-025) and one conducted in Europe in adult patients (Study FG-06-12).

A total of 1,554 patients with moderate or severe atopic dermatitis have been treated in the five core studies. The population evaluated in these studies is representative of the atopic dermatitis population seeking treatment. Of the 607 pediatric (<16 years of age) patients evaluated in the core studies, 330 were 2 to 6 years of age. The amount of body surface area (BSA) affected at baseline varied from 2% to 100%, with most patients affected over more than one-third of their body surface area. Eighty-seven percent of

patients treated the head/neck region. The core studies' population had an adequate gender and racial representation, with nearly an equal percentage of males and females and a substantial (~22%) representation for African Americans. Many of these patients had suffered from atopic dermatitis for most of their lives; disease duration ranged from 0.2 years to 15.9 years in children and 0.2 years to 77.6 years in adults This briefing document will focus on these five core studies.

7.1 Three 12-Week, Double-Blind Studies

7.1.1 Design

Three identically designed, multicenter, randomized, double-blind, parallel group, vehicle-controlled 12-week studies were conducted in the United States (Table 10); one in pediatric patients (Study 97-0-037) and two in adult patients (Studies 97-0-035 and 97-0-036).

Table 10: Three 12-Week, Double-Blind, Phase 3 Studies

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

† Number of patients who were dispensed study drug (= number who received at least one dose of study drug). ‡ Patient No. 84515 was enrolled in this adult study despite being 15 years of age.

Patients applied a thin layer 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 protocol recommended a 1 cm ribbon spread over approximately 100

cm^2 skin surface. Patients were allowed to treat new lesions if they developed. The maximum duration of treatment was 12 weeks. In patients with clearing of atopic dermatitis prior to 12 weeks, treatment was to have continued for 1 week after clearing. There was a 2-week follow-up visit after treatment discontinuation.

Patient selection criteria are detailed in Appendix IV.

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. Blood was collected from patients at Day 1, Week 1, Week 3, and Week 12/end of treatment in order to determine laboratory profiles.

7.1.2 Patient Disposition, Demographics and Other Baseline Characteristics

Patient disposition, and the demographics (other than age) and other baseline characteristics of the patient population for each individual study (two adult and one pediatric) were comparable to that obtained for the combined population. In the text of this briefing document, these data are presented for the three 12-week, double-blind studies combined; the same information for each of the three studies can be found in Appendix III.

A total of 985 patients were randomized (983 dispensed study medication and treated) in the three studies; patient disposition is presented in Table 11.

Table 11: Patient Disposition In The Three 12-Week, Double-Blind Studies Combined

Variable	Treatment Group			Total
	Vehicle	Concentration of Tacrolimus Ointment		
		0.03%	0.1%	
Randomized	330	328	327	985
Intent-to-Treat	328	328	327	983
Completed Treatment	*118 (36%)*	*244 (74%)*	*258 (79%)*	*620 (63%)*
Discontinued	*210 (64%)*	*84 (26%)*	*69 (21%)*	*363 (37%)*
Lack of Efficacy	*141*	*30*	*23*	*194*
Adverse Event	*35*	*19*	*14*	*68*
Administrative	*34*	*35*	*32*	*101*

Intent to Treat Population: all randomized patients who were dispensed study drug.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: NDA 50-777 (Study Reports R98-0214-506-C3-E, L1999000006, and L1999000008 [Tables 13.1.2 and 13.5.8] and Statistical Appendix 8.3.6.1.1).

Demographics and other baseline characteristics are summarized in Table 12. No statistically significant differences among treatment groups were observed with respect to gender, race, age, percent BSA affected, and severity of disease at the start of the study. A total of 55% of the patients were female, and the mean age was 27 years (range 2 to 79 years of age). The majority of patients were white; however, African Americans were well represented, comprising 27% of the patients. Atopic dermatitis affected >50% of the total body surface area at baseline in 41% of patients. The atopic dermatitis was severe in 58% of patients. Eighty-six percent of patients (88% in vehicle group, 86% in 0.03% tacrolimus ointment group, and 83% in 0.1% tacrolimus ointment group) had atopic dermatitis on the head or neck.

Table 12: Baseline Demographics And Patient Characteristics In The Three 12-Week, Double-Blind Studies Combined

Variable		Treatment Group			Total	p-Value†
		Vehicle	Concentration of Tacrolimus Ointment			
			0.03%	0.1%		
Total # of Patients		328	328	327	983	
Pediatric Study		116	117	118	351	
2-6 years of age		*72*	*74*	*69*	*215*	
7-15 years of age		*44*	*43*	*49*	*136*	
Adult Studies‡		212	211	209	632	
Gender	Female	180 (54.9%)	178 (54.3%)	185 (56.6%)	543 (55.2%)	0.828
	Male	148 (45.1%)	150 (45.7%)	142 (43.4%)	440 (44.8%)	
Race	White	218 (66.5%)	220 (67.1%)	214 (65.4%)	652 (66.3%)	0.998
	African Am	85 (25.9%)	87 (26.5%)	89 (27.2%)	261 (26.6%)	
	Oriental	18 (5.5%)	16 (4.9%)	18 (5.5%)	52 (5.3%)	
	Am Indian	2 (0.6%)	1 (0.3%)	1 (0.3%)	4 (0.4%)	
	Other	5 (1.5%)	4 (1.2%)	5 (1.5%)	14 (1.4%)	
Ethnicity	Nonhispanic	314 (95.7%)	320 (97.6%)	310 (94.8%)	944 (96.0%)	0.184
	Hispanic	14 (4.3%)	8 (2.4%)	17 (5.2%)	39 (4.0%)	
Age (yrs)	Mean ± SD	27.0±19.4	26.6±19.0	27.4±19.7	27.0±19.3	0.860
	Median	27	26	25	26	
	Range	2-75	2-76	2-79	2-79	
Severity of AD						0.466
	Moderate	145 (44.2%)	138 (42.1%)	129 (39.5%)	412 (41.9%)	
	Severe	183 (55.8%)	190 (57.9%)	198 (60.6%)	571 (58.1%)	
% BSA Affected						0.730
	Mean ± SD	46.8±26.8	45.1±27	46.2±26.3	46±26.7	
	Median	40.5	39	42	40	
	Range	10-100	10-100	10-100	10-100	
	≥10% to 25%	95 (29.0%)	107 (32.6%)	92 (28.1%)	294 (29.9%)	0.856
	>25% to 50%	98 (29.9%)	91 (27.7%)	98 (30.0%)	287 (29.2%)	
	>50% to 75%	66 (20.1%)	70 (21.3%)	73 (22.3%)	209 (21.3%)	
	>75% to 100%	69 (21.0%)	60 (18.3%)	64 (19.6%)	193 (19.6%)	

Intent to Treat Population: all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug). SD: standard deviation. AD: Atopic dermatitis. BSA: body surface area. † Chi-squared test for discrete variables and one-way ANOVA with treatment as source of variation for continuous variables. ‡ Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. For study based analyses, this patient is considered an adult; for age-based analyses, this patient is categorized by true age. Source: NDA 50-777 (Statistical Appendix 8.3.6.2.1).

7.1.3 Drug Exposure

Drug exposure for each individual study (two adult and one pediatric) was comparable to that obtained for the combined population. In the text of this briefing document, drug exposure data are presented for the three 12-week, double-blind studies combined; the same information for each of the three studies can be found in Appendix III.

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

The mean [median] number of treatment days in the 12-week (84-day) studies was 43 [25.5] in the vehicle treatment group and 70 [84, 0.03%; 85, 0.1%] in each of the tacrolimus ointment treatment groups. There were no notable age differences in the length of treatment in the tacrolimus ointment treatment groups. The lower number of treatment days in the vehicle group is due to the higher percentage of premature discontinuations in the vehicle group (primarily due to lack of efficacy) compared with the tacrolimus groups. Treatment days are summarized in Table 13.

The mean total amount of ointment used during the three 12-week, double-blind studies was 272 grams (range 3-2201 grams) for the vehicle group, compared with 381 grams (range 0-2816 grams) and 390 grams (range 1-2497 grams) for the 0.03% and 0.1% tacrolimus ointment treatment groups, respectively. This represents a mean total amount of tacrolimus applied of 114 mg (range 0-845 mg) and 390 mg (range 1-2497 mg) in the 0.03% and 0.1% tacrolimus ointment treatment groups, respectively. The differences in the total amount of ointment used among the three treatment groups is consistent with the

shorter duration of treatment in the vehicle group due to the higher percentage of discontinuations.

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

Table 13: Treatment Days: Three 12-Week, Double-Blind Studies Combined

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
All Patients	n	328	328	325‡
	Mean ± SD	43.2 ± 34.8	70.5 ± 26.8	70.1 ± 28.7
	Median	25.5	84.0	85.0
	Range	1-118	1-133	1-134
Pediatric Patients†	n	116	118	118
	Mean ± SD	49.1 ± 34.7	72.4 ± 26.9	73.6 ± 26.5
	Median	46.5	85.0	85.0
	Range	1-93	1-133	1-134
2-6 years of age	*n*	*72*	*74*	*69*
	Mean ± SD	*50.6 ± 35.5*	*72.3 ± 26.8*	*72.0 ± 28.1*
	Median	*63.5*	*85.0*	*84.0*
	Range	*1-92*	*1-133*	*1-134*
7-15 years of age†	*n*	*44*	*44*	*49*
	Mean ± SD	*46.6 ± 33.6*	*72.6 ± 27.3*	*76.0 ± 24.1*
	Median	*25.5*	*85.0*	*85.0*
	Range	*2-93*	*1-94*	*7-99*
Adult Patients†	n	212	210	207‡
	Mean ± SD	40.0 ± 34.5	69.4 ± 26.8	68.1 ± 29.7
	Median	22.0	84.0	84.0
	Range	1-118	1-102	1-101

Intent to Treat Population: all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug).
SD: standard deviation.
† Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. For this table, this patient is categorized by true age.
‡ Two patients did not have complete treatment day information.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: NDA 50-777 (Statistical Appendices 8.4.13.3.1, 8.4.13.3.2, 8.4.13.3.3, 8.4.13.3.4, and 8.4.13.3.5).

7.2 Two Long-Term Safety Studies

7.2.1 Design

Two Phase 3, multicenter, open-label, single concentration (0.1% tacrolimus ointment), long-term (up to 12 months) studies were conducted; one in the United States in pediatric patients (Study 96-0-025) and one in Europe in adult patients (Study FG-06-12).

Table 14: Long-Term Safety Studies

Study	Description	Patients [actual age]	Regimen	n†
96-0-025 [US] [R98-0213-506-C3-E]	Open label, single concentration, long-term, multicenter study	Children with moderate or severe atopic dermatitis [aged 2-15 years]	Tacrolimus (0.1%) ointment twice daily for up to 1 year	255
FG-06-12 [Europe] [FG98-506-07]	Open label, single concentration, long-term, multicenter study	Adults with moderate or severe atopic dermatitis [aged 18-70 years]	Tacrolimus (0.1%) ointment twice daily for up to 1 year	318‡

† Patient population: all enrolled patients who were dispensed study drug.
‡ Two of these patients did not have data beyond baseline and were excluded from safety analyses.
[Note: these were not extension patients]

A thin layer of 0.1% tacrolimus ointment was applied twice daily to areas of active disease. The protocol recommended a 1 cm ribbon spread over approximately 100 cm^2 skin surface. Areas of active disease were defined by the investigator at each visit, or as determined by the patient or parent/guardian during the course of the study after discussion with the physician. During each episode of atopic dermatitis, treatment was to have continued until approximately 1 week after complete clearance of the disease as determined by the physician.

In Study 96-0-025, patients were evaluated at least six times during the 1-year study period: at baseline (Day 1), Week 1, and Months 3, 6, 9, and 12 or end of study, if less than 12 months. Scheduled evaluations were performed regardless of whether the disease was active or in remission. In addition to these scheduled visits, patients were to be evaluated each time remission was achieved (approximately 7 days after disease cleared), each time treatment resumed due to recurrence, and 1 week following resumption of treatment. Adverse events were recorded during the course of the study. Blood and urine were to be collected on Day 1 and at Months 6 and 12/end of study in order to determine laboratory profiles. To aid in data collection, patients or parents/guardians were asked to record drug application information, deviation from instructions, the use of concomitant medications, and any symptoms, complaints, illnesses or accidents in a patient diary during the study.

Study FG-06-12 consisted of a screening visit (within 30 days before the baseline visit), a baseline visit (Day 1), a visit 1, 2, and 4 weeks after treatment began, monthly visits thereafter, and unscheduled visits if the patient experienced a severe flare-up of atopic dermatitis or other medical problem. Safety assessments during the study included monitoring for adverse events (with infection selected as a special-interest adverse event), laboratory assessments (hematology, clinical chemistry, and renal and hepatic function), and immunocompetence assessments (CD4 and CD8 counts and the Recall Antigen Test).

The two long-term safety studies were designed so that planned enrollment would fulfill the ICH Guideline for long-term exposure studies. As a further assurance of sufficient enrollment to meet the ICH Guideline, patients in Study FG-06-12 were prospectively assigned to participate for either 6 or 12 months. Patient selection criteria are summarized in Appendix IV.

7.2.2 Patient Disposition, Demographics and Other Baseline Characteristics

Patient disposition is summarized in Table 15 and Table 16.

Table 15: Patient Disposition-Pediatric Long-Term Study 96-0-025

	Number (%) Patients
Screened	313
Enrolled	255
Intent to Treat Population[†]	255
Prematurely Discontinued	66 (25.9%)
Prematurely Discontinued due to:	
Any Adverse Event	10 (3.9%)
Application Site Adverse Event	5 (2.0%)
Nonapplication Site Adverse Event	5 (2.0%)
Lack of Efficacy	8 (3.1%)
Administrative Reason[#]	48 (18.8%)
Discontinuation Day for 66 patients who withdrew	
Mean ± standard deviation	162.7 ± 99.5
Median	133
Range	7 - 411

[†] All enrolled patients who received at least one dose of study drug.
[#] Administrative reasons included lost to follow-up, non-compliance, patient refusal, etc.
Source: NDA 50-777, Study Report R98-0213-506-C3-E (Tables 13.1.1, 13.1.2, 13.5.12.1, 13.5.12.2, and 13.5.12.3, and Appendix 14.4.1.1.)

Table 16: Patient Disposition-Adult Long-Term Study FG-06-12

	Planned Exposure		Total
	6 Months (n = 200)	12 Months (n=116)	(n =316)
Completed study	153 (76.5)	92 (79.3)	245 (77.5)
Reasons for withdrawal‡			
Lack of efficacy	10 (5.0)	9 (7.8)	19 (6.0)
Requirement for topical steroids	10 (5.0)	3 (2.6)	13 (4.1)
Adverse event	8 (4.0)	5 (4.3)	13 (4.1)
Lost to follow-up	8 (4.0)	3 (2.6)	11 (3.5)
Noncompliance	5 (2.5)	1 (0.9)	6 (1.9)
Withdrawal of consent	3 (1.5)	0	3 (0.9)
Pregnancy	1 (0.5)	2 (1.7)	3 (0.9)
Other	2 (1.0)	1 (0.9)	3 (0.9)
Total withdrawn from study	47 (23.5)	24 (20.7)	71 (22.5)
Day of withdrawal for patients who withdrew			
Mean ± SD	89.9±56.2	147.5±107.9	109.3±81.6
Minimum – maximum	7 – 223	15 –343	7 –343

‡ Reasons for withdrawal as assessed by the investigator
Source: NDA 50-777, Study Report FG98-506-07 (Table 13.1.2).

Demographics and other baseline characteristics are summarized in Table 17.

Table 17: Patient Demographics And Other Baseline Characteristics In Long-Term Studies: Pediatric Study 96-0-025 And Adult Study FG-06-12

		Study 96-0-025 Pediatric Patients	Study FG-06-12 Adult Patients
Total Number of Patients		255†	316‡
Age (years)	Mean ± SD	7.6 ± 3.9	31.1 ±11.0
	Median (range)	7 (2 - 15)	28 (18-70)
Gender	Male	123 (48.2%)	141 (44.6%)
	Female	132 (51.8%)	175 (55.4%)
Race	White	161 (63.1%)	303 (95.9%)
	African Am	71 (27.8%)	6 (1.9%)
	Oriental	13 (5.1%)	7 (2.2%)
	Other	10 (3.9%)	0
Severity of Atopic Dermatitis:	Moderate	133 (52.2%)	149 (47.2%)
	Severe	122 (47.8%)	167 (52.8%)
% Body Surface Area Affected:	2 - 6 years:		
	n	115	
	Mean ± SD	42.7 ± 26.4	
	Median (range)	36.0 (2.4 - 99.4)	34.7 ± 17.3
	7 - 15 years:		35.6 (6-96)
	n	140	
	Mean ± SD	39.4 ± 23.6	
	Median (range)	35.2 (2.6 - 99.2)	
Affected on Head/Neck		203 (79.6%)	301 (95.3%)
Atopic Dermatitis Duration			
Current Episode (months)	Mean ± SD	35.9 ± 44.5	72.5 ±124.9±19.5 (0.3-
	Median (range)	17.1 (0.5 - 193.6)	603.1)
Disease Duration (years)	Mean ± SD	6.4 ± 3.7	25.0 ±13.0
	Median (range)	5.5 (0.3 - 15.9)	23.0 (2-70)

Patient population: † all enrolled patients who were dispensed study drug (= all enrolled patients who received at least one dose of study drug). ‡ All enrolled patients who were dispensed study drug (= all enrolled patients who received at least one dose of study drug) and had postbaseline data.
Severity: Rajka & Langeland criteria SD: standard deviation.
Source: NDA 50-777 (Study Report R98-0213-506-C3-E and Study Report FG98-506-07)

7.2.3 Exposure

Exposure to tacrolimus ointment in the long-term studies is summarized in Table 18.

Patients in both studies applied ointment on most days of study participation.

Table 18: Summary Of Exposure To Tacrolimus In Long-Term Studies: Pediatric Study 96-0-025 And Adult Study FG-06-12

		Study 96-0-025 Pediatric Patients	Study FG-06-12 Adult Patients
Total Number of Patients		255†	316‡
Percent BSA Treated at Start of Therapy§			
2 - 6 years	n	115	
	Mean ± SD	42.3 ± 26.2	-----
	Median (range)	35.7 (2.4-99.4)	
7 - 15 years	n	140	
	Mean ± SD	39.2 ± 23.4	-----
	Median (range)	35.2 (2.6-99.2)	
≥18 years	n		302
	Mean ± SD	-----	30.3 ± 17.4
	Median (range)		29.2 (0.0-66.0)
Total Number of Days of Treatment			
	n	255	313¶
	Mean ± SD	279.3 ± 114.3	186.6 ± 94.9
	Median (range)	338 (2-425)	170 (7-381)
			6-month group: 197
			138.3 ± 86.6
			155 (7-208)
			12-month group: 116
			268.7 ± 85.9
			303 (15-381)
Days of Treatment as % of No. of Days in Study			
	n	255	313¶
	Mean ± SD	87.1 ± 20.8	86.4 ± 16.8
	Median (range)	97 (7-100)	94.5 (12-100)

SD: standard deviation. BSA: body surface area. † all enrolled patients who were dispensed study drug (= all enrolled patients who received at least one dose of study drug). ‡ All enrolled patients who were dispensed study drug (= all enrolled patients who received at least one dose of study drug) and had postbaseline data. § In Study 96-0-025, %BSA to be treated at baseline and in Study FG-06-12, %BSA treated during Week 1. ¶ Three patients had no diary information. Other patients were assumed to have applied ointment on days with missing diary information. Source: NDA 50-777 (Study Report R98-0213-506-C3-E and Study Report FG98-506-07).

8 EFFICACY

8.1 Three 12-Week, Double-Blind Studies

The primary efficacy endpoint was the incidence of success obtained from the Physician's Global Evaluation of Clinical Response (*Physician's Global*) at the end of treatment. For the Physician's Global, change from baseline in overall atopic dermatitis status was rated using the following 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 (≥90% improvement) in areas defined for treatment at baseline.

Secondary endpoints included:

- *Eczema Area and Severity Index (EASI) score*

  The EASI was developed by Dr. Jon M. Hanifin in order to provide an overall measure of the severity of the disease. EASI is a composite score calculated 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 4 predefined body regions--head and neck, trunk, upper limbs, and lower limbs. The highest possible EASI score is 72.

- *Percentage of body surface area affected (%BSA affected)*

  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.

- *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. A representative score (defined as the sum of the individual scores for all body regions treated at baseline divided by the number of regions treated at baseline for each of the six clinical signs) was determined. The sum of the representative scores for each of the six clinical signs plus the pruritus score (analog scale score converted to a 4-point score) was defined as the Total Score (highest possible total score = 21).

- *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."

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); i.e., all randomized patients who were dispensed the treatment medication. Therefore, the primary patient population for efficacy analyses in NDA 50-777 and in this briefing document is the ITT population.

In each individual study, Fisher's exact test (Studies 97-0-035 and 97-0-036) or Cochran-Mantel-Haenszel test stratified by age group (Study 97-0-037) 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 all three studies, Fisher's exact test (Studies 97-0-035 and 97-0-036) or Cochran-Mantel-Haenszel test stratified by age group (Study 97-0-037) was used for the pairwise comparison of the three treatment groups, each at the 5% level of significance.

For combined analysis of success, the Cochran-Mantel-Haenszel test, controlling for study, was used to determine if there was a difference among the three treatment groups and, when this occurred, to determine if there were differences when each pair of treatment groups was analyzed separately. In addition, the Breslow-Day statistic tested for homogeneity across studies within each of the three pairwise comparisons.

For secondary efficacy endpoints (Physician's Assessment of Individual Signs, % BSA affected, EASI Score, Total Clinical Score, Patient's Assessment of Pruritus), changes

from baseline to the end of treatment were analyzed using general linear models; least squares means (LS mean) and their standard errors were calculated based on the model. The model included treatment groups, study and baseline value for combined analysis, and treatment group, age group, and baseline value for analysis for pediatric patients.

Since the pediatric population is of particular interest and the efficacy results for the adult population mirrored that for all patients, this briefing document will focus on all patients (adult and pediatric studies) and pediatric patients (pediatric study 97-0-037).

8.1.1 All Patients

Tacrolimus ointment (0.03% and 0.1%) was effective in both children (2 years to 15 years of age) and adults (≥16 years of age). In the three studies combined (Studies 97-0-037, 97-0-035, 97-0-036), both concentrations of tacrolimus ointment were statistically significantly more effective than vehicle control for all efficacy parameters tested.

8.1.1.1 Success (Physician's Global Evaluation of Clinical Response)

In each of the three 12-week double-blind studies, and when data from these studies were combined, both concentrations of tacrolimus ointment had a statistically significantly higher success rate than vehicle (Table 19 and Table 20 and Figure 4). The success rate was 4- to 5-fold higher in tacrolimus ointment-treated patients compared with vehicle-treated patients. The Breslow-Day statistic tested for homogeneity across studies indicated no treatment by study interactions ($p>0.15$).

Data from the three 12-week double-blind studies combined demonstrated that the 0.1% tacrolimus ointment concentration provided a greater therapeutic benefit than the 0.03% tacrolimus ointment concentration as evidenced by a statistically significantly higher success rate (Table 20). This is discussed in further detail in Section 8.2.

Table 19: Success Rate (³ 90% Improvement) At The End Of Treatment In Each 12-Week, Double-Blind Study

Study	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Pediatric Study 97-0-037	8/116 (6.9%)	42/117 (35.9%)	48/118 (40.7%)
Adult Studies			
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%)

	p-Value§			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Pediatric Study 97-0-037	<0.001	<0.001	<0.001	0.401
Adult Studies				
97-0-035†	<0.001	<0.001	<0.001	0.369
97-0-036	<0.001	<0.001	<0.001	0.060

Population: intent-to-treat; all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug).
† Patient No. 84515 was enrolled/randomized in adult Study 97-0-035 despite being 15 years of age. For all efficacy analyses except for age-based analyses, this patient is considered an adult patient.
§P-values for patients in pediatric study are from Cochran-Mantel-Haenszel statistics stratified by age. For individual study results for Studies 97-0-035 and 97-0-036, p-values are from Fisher's exact test. Statistical significance is indicated by p-values ≤0.05.
Success = cleared or excellent improvement (≥90% improvement) based on Physician's Global.
Source: NDA 50-777 (Study Reports R98-0214-506-C3-E, L1999000006, and L1999000008 [Table 13.4.1.1] and Statistical Appendices 8.3.6.3.1 and 8.3.6.3.2).

Figure 4: Success Rate By Study for the Three 12-Week Double-Blind Studies

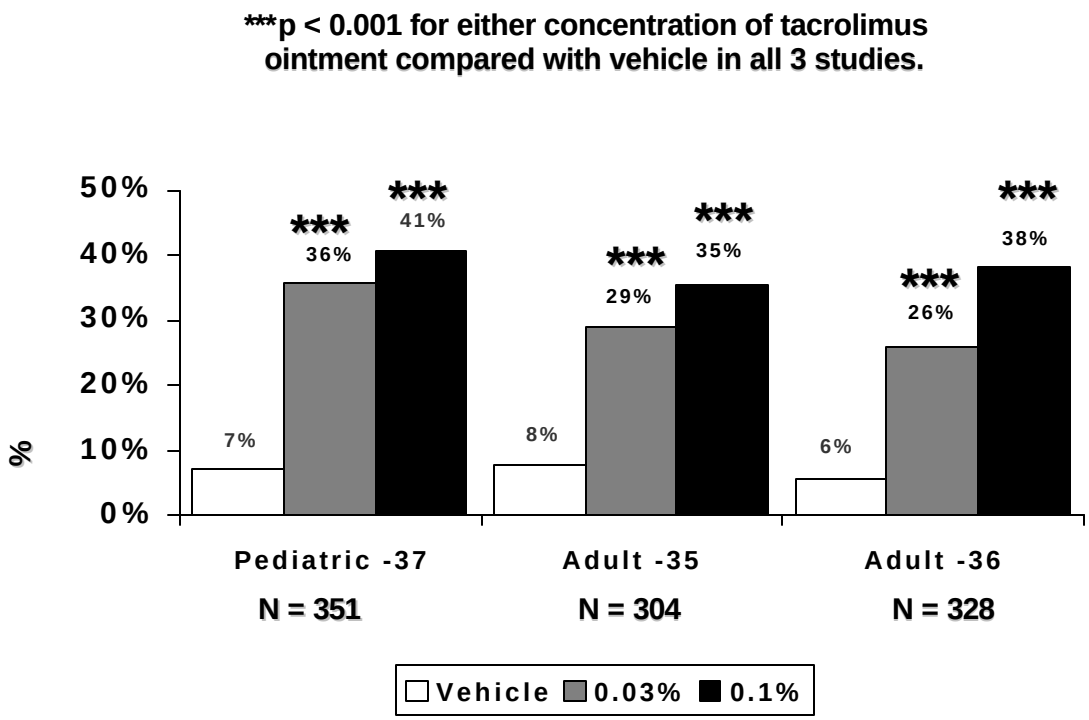


Table 20: Success Rate (³ 90% Improvement) At The End Of Treatment For The Three 12-Week, Double-Blind Studies

Study	Treatment Group		
	Vehicle	Concentration of Tacrolimus Ointment	
		0.03%	0.1%
Patients in All Studies	22/328 (6.7%)	100/328 (30.5%)	125/327 (38.2%)
Pediatric Study	8/116 (6.9%)	42/117 (35.9%)	48/118 (40.7%)
Adult Studies†	14/212 (6.6%)	58/211 (27.5%)	77/209 (36.8%)

	p-Value§			
	Overall	0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Patients in All Studies	<0.001	<0.001	<0.001	0.038
Pediatric Study	<0.001	<0.001	<0.001	0.401
Adult Studies†	<0.001	<0.001	<0.001	0.041

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

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

§P-values for patients in all studies, pediatric study, and adult studies combined are from Cochran-Mantel-Haenszel statistics stratified by study (overall, adult studies) or age (pediatric study). Statistical significance is indicated by p-values ≤0.05.

Success = cleared or excellent improvement (≥90% improvement) based on Physician's Global.

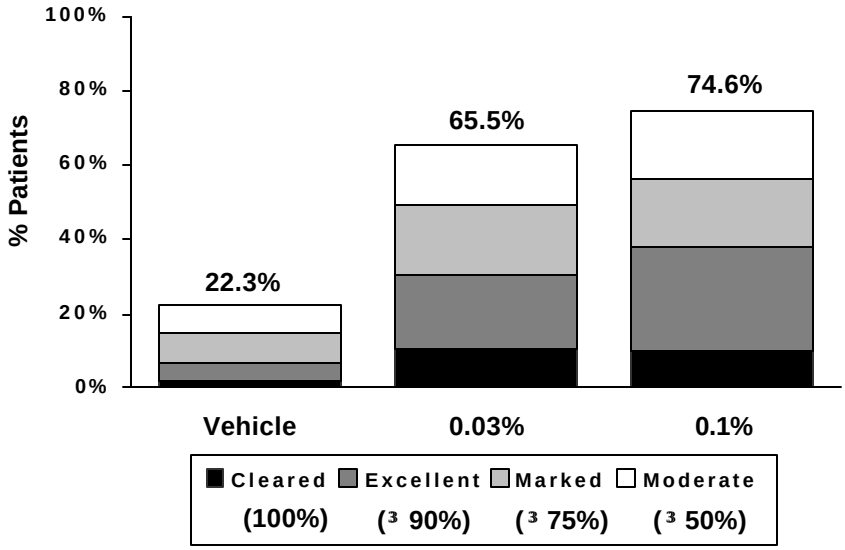
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).

Source: NDA 50-777 (Study Reports R98-0214-506-C3-E, L1999000006, and L1999000008 [Table 13.4.1.1] and Statistical Appendices 8.3.6.3.1 and 8.3.6.3.2).

The success criterion of ≥90% improvement from baseline based on the Physician's Global Evaluation of Clinical Response is very stringent. Clinically, at least moderate improvement (≥ 50% improvement from baseline) presents a substantial benefit to the patient. Cumulative improvement rates for the three 12-week, double-blind studies combined are summarized in Figure 5.

Figure 5: Cumulative Improvement In Atopic Dermatitis Based on Physician's Global Evaluation of Clinical Response: All Patients In 12-Week, Double-Blind Studies

[p<0.001 0.03% tacrolimus ointment versus vehicle,
0.1% tacrolimus ointment versus vehicle]
[p=0.011 0.1% versus 0.03% tacrolimus ointment]



8.1.1.2 Secondary Efficacy Parameters

Improvement in disease status with application of tacrolimus ointment (either 0.03% or 0.1%) was also evidenced by reductions in EASI score, Physician's Assessment of Individual Signs of Atopic Dermatitis (Total Score as well as Representative Score for each sign), %BSA affected, and Patient's Assessment of Pruritus (Figure 6, Figure 7, Figure 8, Figure 9).

8.1.1.3 Rapid Improvement

Substantial improvement was rapidly observed with both concentrations of tacrolimus ointment, generally during the first week of treatment (e.g., Figure 10).

Figure 6: Change From Baseline To The End Of Treatment For Individual Signs Of Atopic Dermatitis: All Patients In 12-Week, Double-Blind Studies

[Least Squares Mean and Standard Error based on the general linear model including treatment group, study and baseline value]

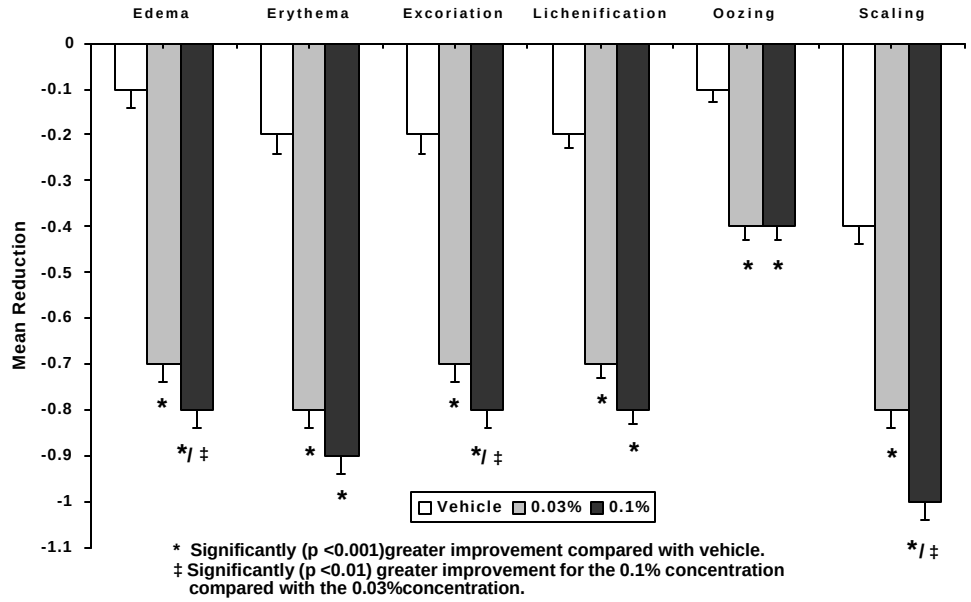
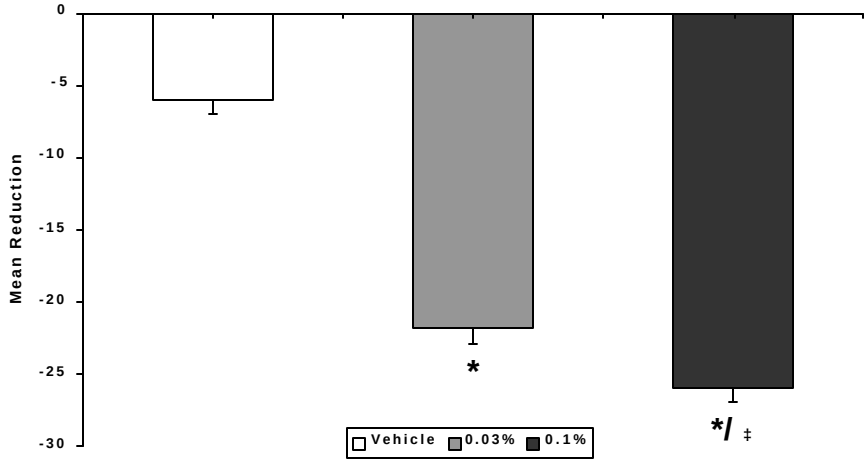


Figure 7: Change From Baseline To The End Of Treatment For Percent BSA Affected: All Patients In 12-Week, Double-Blind Studies

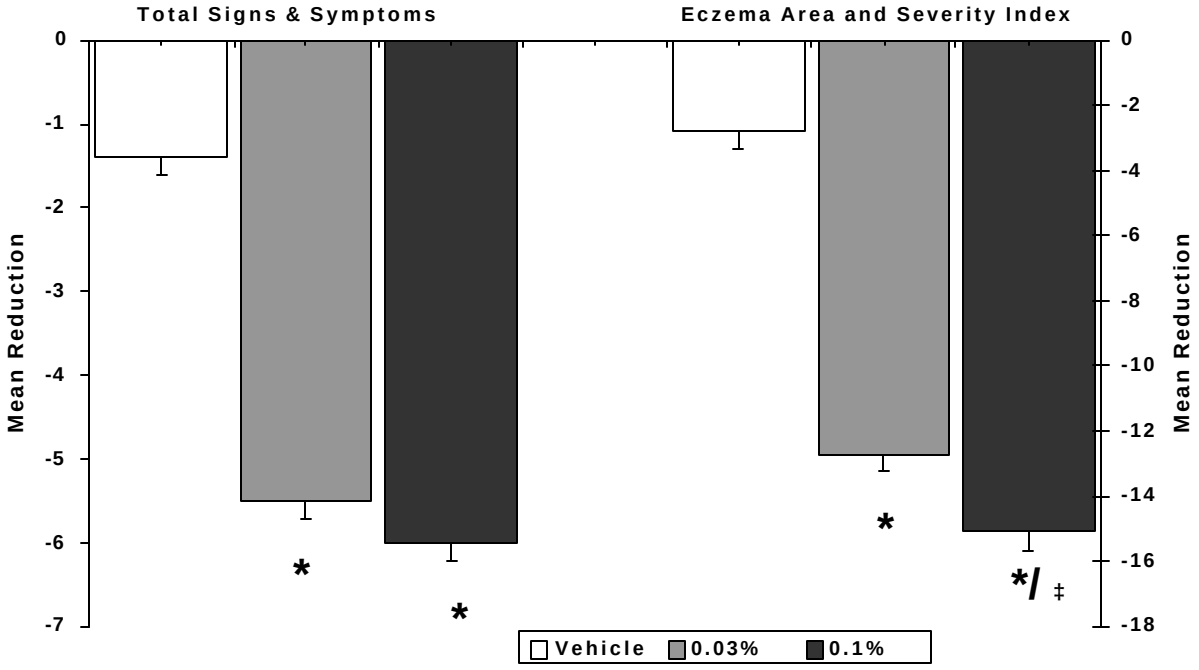
[Least Squares Mean and Standard Error based on the general linear model including treatment group, study and baseline value]



* Significantly (p <0.001)greater improvement compared with vehicle.
‡ Significantly (p <0.01) greater improvement for the 0.1% concentration compared with the 0.03%concentration.

Figure 8: Change From Baseline To The End Of Treatment: Total Score For Signs Of Atopic Dermatitis And Eczema Area And Severity Index (EASI) Score: All Patients In 12-Week, Double-Blind Studies

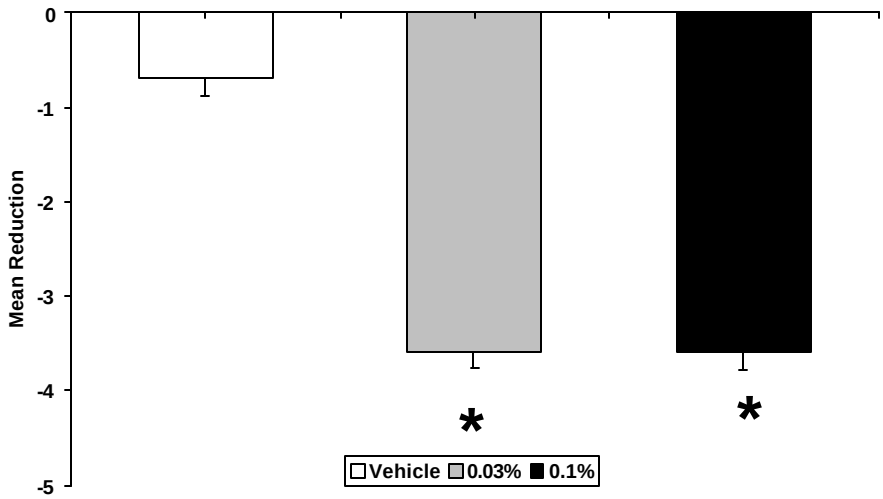
[Least Squares Mean and Standard Error based on the general linear model including treatment group, study and baseline value]



*** Significantly (p <0.001)greater improvement compared with vehicle.**
‡ Significantly (p <0.01) greater improvement for the 0.1% concentration compared with the 0.03%concentrations.

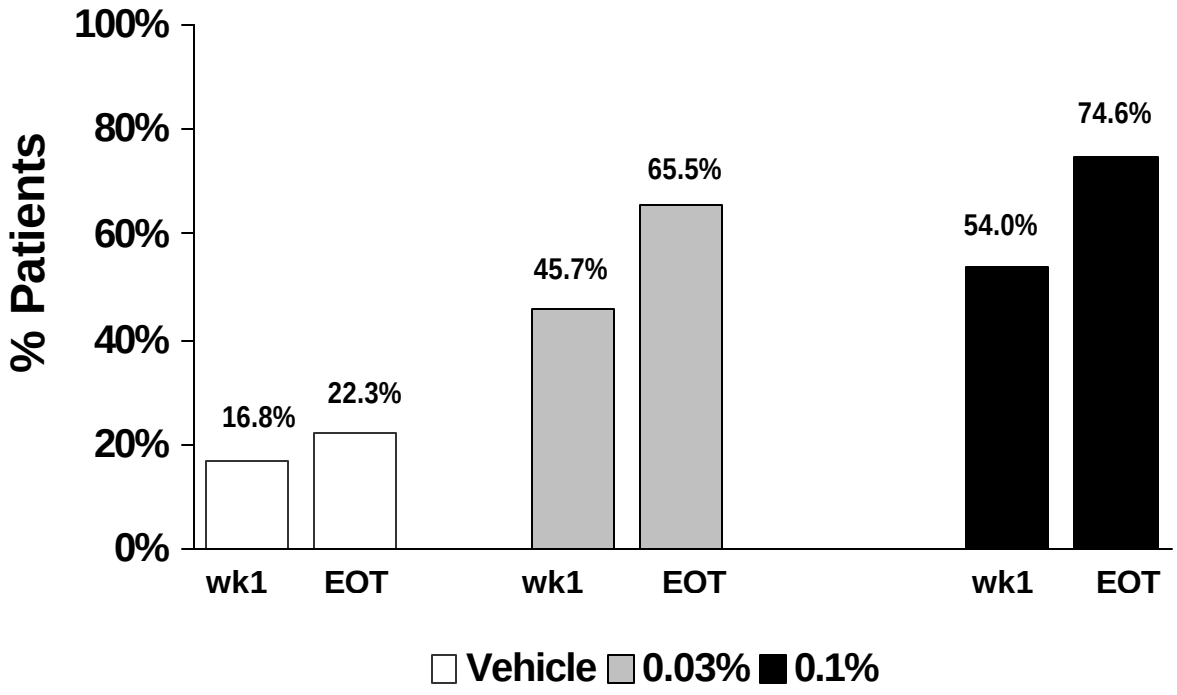
Figure 9: Change From Baseline To The End Of Treatment For Pruritus: All Patients In 12-Week, Double-Blind Studies

[Least Squares Mean and Standard Error based on the general linear model including treatment group, study and baseline value]



* Significantly ($p < 0.001$) greater improvement compared with vehicle.

Figure 10: At Least Moderate Improvement (³50% Improvement) Based on Physician's Global Evaluation of Clinical Response at Week 1 and End of Treatment: All Patients in 12-Week, Double-Blind Studies



8.1.2 Pediatric Study

Based on success rate (≥90% improvement) at the end of treatment, both the 0.03% and 0.1% concentrations of tacrolimus ointment were significantly more effective than vehicle for the treatment of atopic dermatitis in pediatric patients (Table 19). Also of clinical relevance, a total of 73% (85/117) of pediatric patients treated with 0.03% tacrolimus ointment and 78% (92/118) of pediatric patients treated with 0.1% tacrolimus ointment had at least moderate improvement (≥50% improvement) at the end of treatment compared with 27% (31/116) of vehicle-treated patients (Figure 11).

Greater improvement (as represented by decreased score) in EASI Score, Total Score (as well as representative score for each individual sign and symptom [edema, erythema, excoriation, lichenification, oozing, and scaling], Figure 12), percent BSA affected and patient assessment of pruritus was also observed for each tacrolimus ointment treatment group compared with the vehicle group.

Figure 11: Cumulative Improvement In Atopic Dermatitis Based on Physician's Global Evaluation of Clinical Response: Pediatric Study

[p<0.001 for 0.03% tacrolimus ointment versus vehicle]

[p<0.001 for 0.1% tacrolimus ointment versus vehicle]

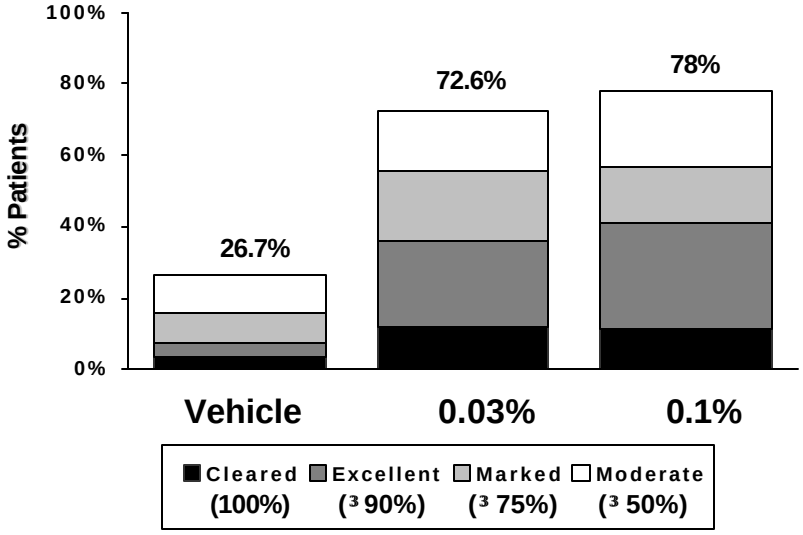
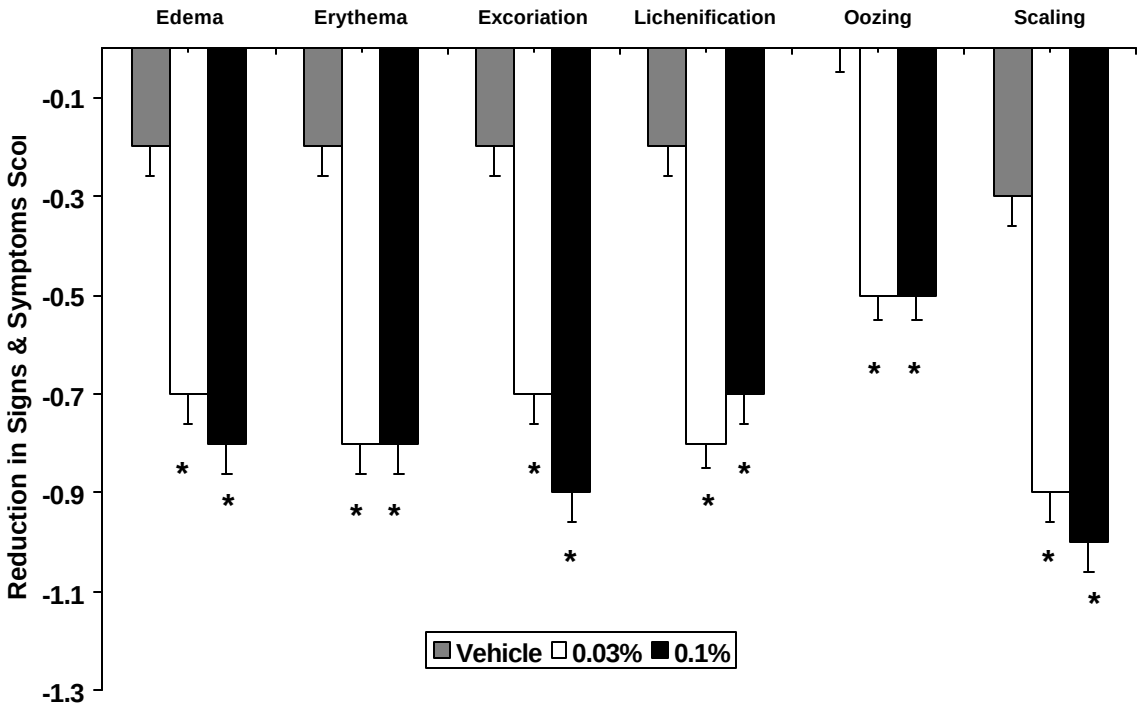


Figure 12: Change From Baseline To The End Of Treatment For Individual Signs Of Atopic Dermatitis: Pediatric Study

[Least Squares Mean and Standard Error based on the general linear model including treatment group, age group and baseline value]



*Significantly ($p<0.001$) greater improvement compared with vehicle

8.2 Comparison of 0.1% versus 0.03% Tacrolimus Ointment: Efficacy

In each individual Phase 3, 12-week double-blind study, the success rate was numerically higher for the 0.1% tacrolimus ointment group compared with the 0.03% concentration group. This result was consistent across all three studies.

When data from all three studies was combined, the 0.1% tacrolimus ointment concentration was more effective than the 0.03% tacrolimus ointment concentration based on primary and secondary efficacy parameters. Statistically significantly more patients achieved ≥90% clinical improvement with 0.1% tacrolimus ointment compared with 0.03% tacrolimus ointment (Table 20, Table 21). The 0.1% tacrolimus ointment concentration was also more effective than the 0.03% concentration based on the distribution of responses in the Physician's Global Evaluation. Clinically relevant moderate improvement or better (≥ 50% improvement) was observed in 66% of patients in the 0.03% tacrolimus ointment group and 75% in the 0.1% tacrolimus ointment group (p=0.011; Figure 13).

The 0.1% tacrolimus ointment concentration was statistically more effective than the 0.03% concentration for improvement in EASI score; representative scores for edema, excoriation, and scaling; and percent BSA affected (Figure 6, Figure 7, Figure 8). A trend toward greater improvement with the 0.1% tacrolimus ointment concentration was observed with respect to Total Score for the individual signs of atopic dermatitis.

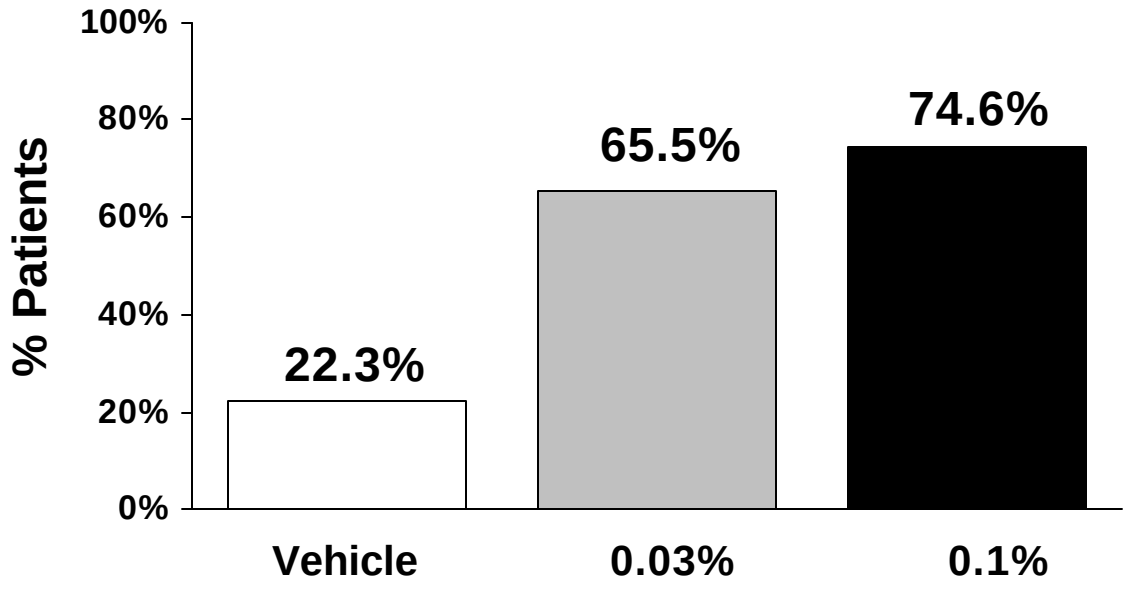
The greater therapeutic benefit of 0.1% tacrolimus ointment compared with the 0.03% concentration was particularly evident in adult patients, and patients with severe atopic dermatitis at baseline and those with extensive (≥ 75% BSA affected) disease involvement (Table 21, Figure 14, Figure 15).

Table 21: Success (³ 90% Improvement) Rate At The End Of Treatment For The Tacrolimus Ointment Groups In The Three 12-Week, Double-Blind Studies Combined: Subsets of Interest

	0.03%	0.1%	p-Value CMH† 0.03% vs 0.1%
Patients in All Studies	100/328 (30.5%)	125/327 (38.2%)	0.038
Severity of AD at Baseline			
Moderate	55/138 (39.9%)	54/129 (41.9%)	0.839
Severe	45/190 (23.7%)	71/198 (35.9%)	0.010
% Affected BSA at Baseline			
≥10% - ≤25%	48/107 (44.9%)	42/92 (45.7%)	0.960
>25% - ≤50%	29/91 (31.9%)	40/98 (40.8%)	0.266
>50% - ≤75%	18/70 (25.7%)	26/73 (35.6%)	0.246
>75% - 100%	5/60 (8.3%)	17/64 (26.6%)	0.010

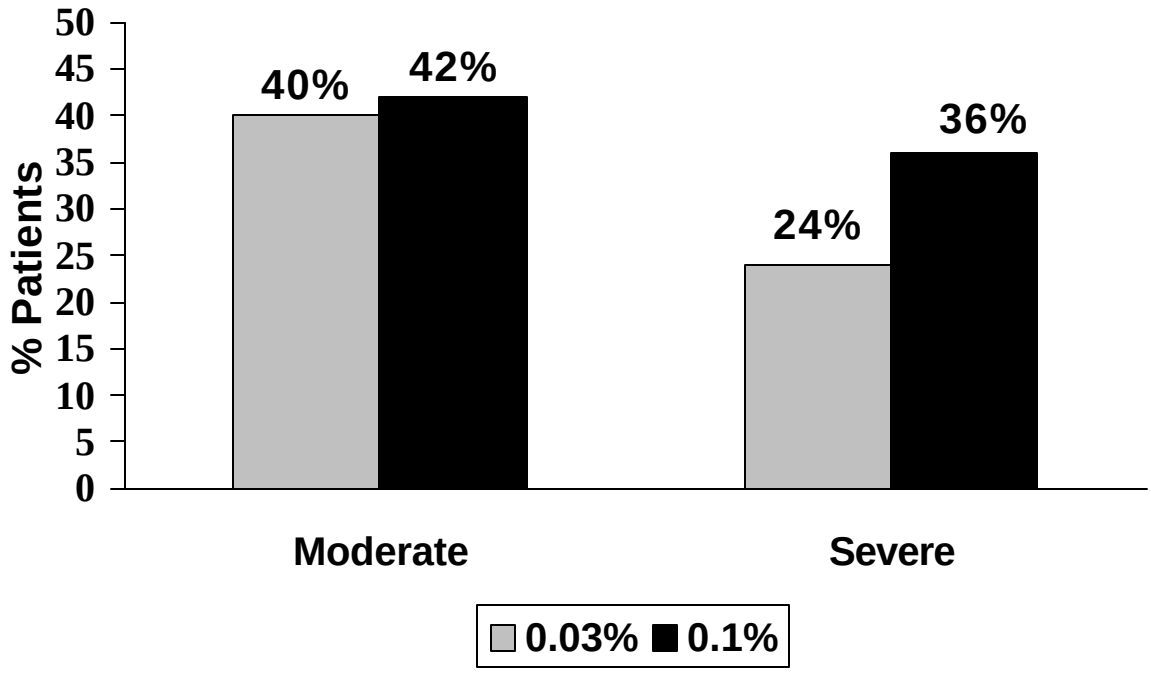
Patient Population: intent-to-treat; all randomized patients who were dispensed study drug (= all randomized patients who received at least one dose of study drug).
Success = cleared or excellent improvement (≥90% improvement) based on Physician's Global.
AD: Atopic dermatitis. BSA: Body surface area affected by atopic dermatitis.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
† CMH: Cochran-Mantel-Haenszel Statistics stratified by study. Statistical significance is indicated by p-values ≤0.05.
Source: NDA 50-777 (Statistical Appendices 8.3.6.4.1).

Figure 13: At Least Moderate Improvement (³50% Improvement) Based on Physician's Global Evaluation of Clinical Response: All Patients in 12-Week, Double-Blind Studies



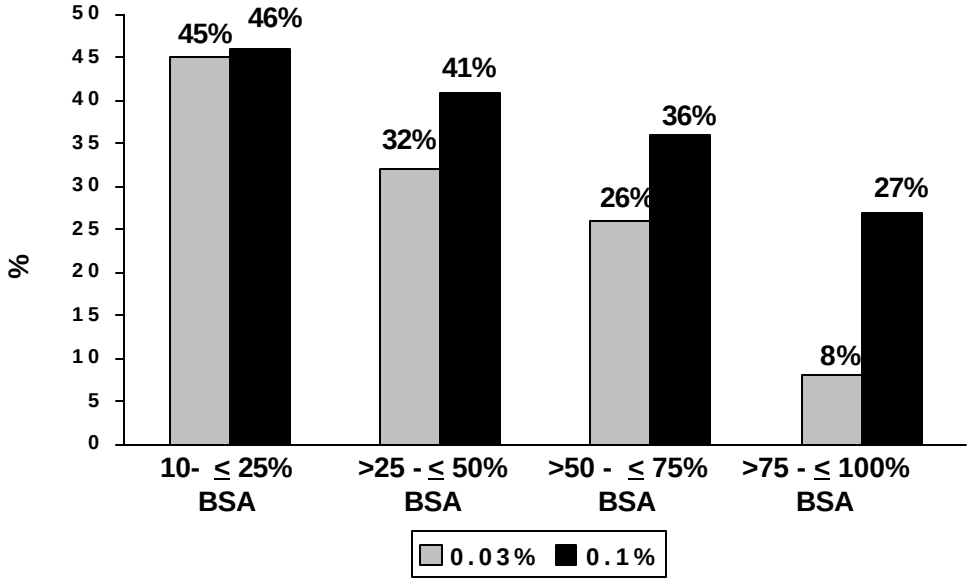
p = 0.011, 0.1% tacrolimus ointment versus 0.03% tacrolimus ointment

Figure 14: Success Rate With 0.1% and 0.03% Tacrolimus Ointment Concentrations by Baseline Disease Severity



p=0.010 for 0.1% tacrolimus ointment versus 0.03% tacrolimus ointment, severe disease

Figure 15: Success Rate With 0.1% and 0.03% Tacrolimus Ointment Concentrations by Baseline Percent BSA Affected



p=0.010 for 0.1% tacrolimus ointment versus 0.03% tacrolimus ointment, >75% to 100% BSA affected at baseline

The data also suggest a greater therapeutic benefit with the 0.1% tacrolimus ointment concentration compared with the 0.03% concentration for African American adults. For African American adult patients, those administered the 0.1% tacrolimus ointment concentration had a numerically higher success rate than those applying 0.03% tacrolimus ointment (29% versus 16%).

8.3 Two Long-Term Safety Studies

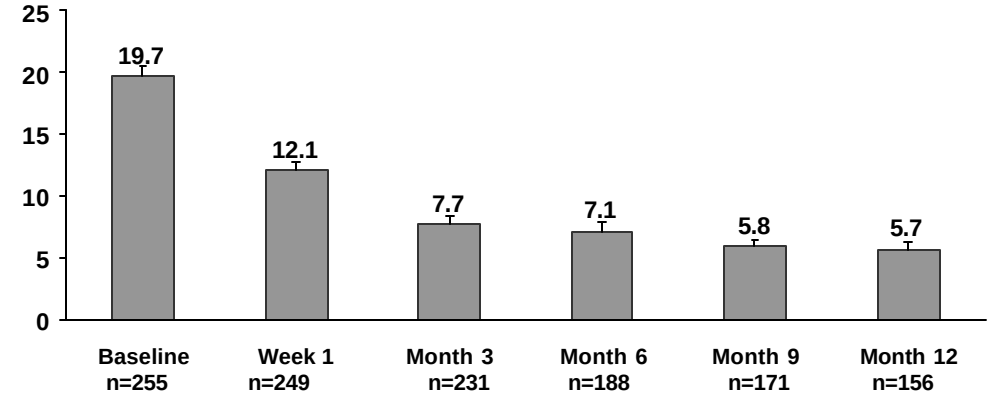
Although the primary focus of these studies was safety, efficacy was also evaluated based on physician assessments (Physician's Assessment of Individual Signs of Atopic Dermatitis, %BSA affected), a patient assessment (Patient's Assessment of Pruritus), and the composite EASI score.

Children (2 to 15 years of age) and adults all showed a rapid (within 1 week) improvement in their disease status as indicated by a reduced score for the efficacy parameters. (For example, Figure 16 and Figure 17 show EASI score and pruritus assessment for the pediatric and adult long-term safety studies.) This improvement was at least maintained during the rest of the 1-year study. There was no indication that the effectiveness of tacrolimus ointment decreased with prolonged daily use.

Figure 16: EASI Score By Visit: Long-Term Safety Studies

Pediatric Safety Study 96-0-025

Mean ±SE



Adult Safety Study FG-06-12

Mean ±SE

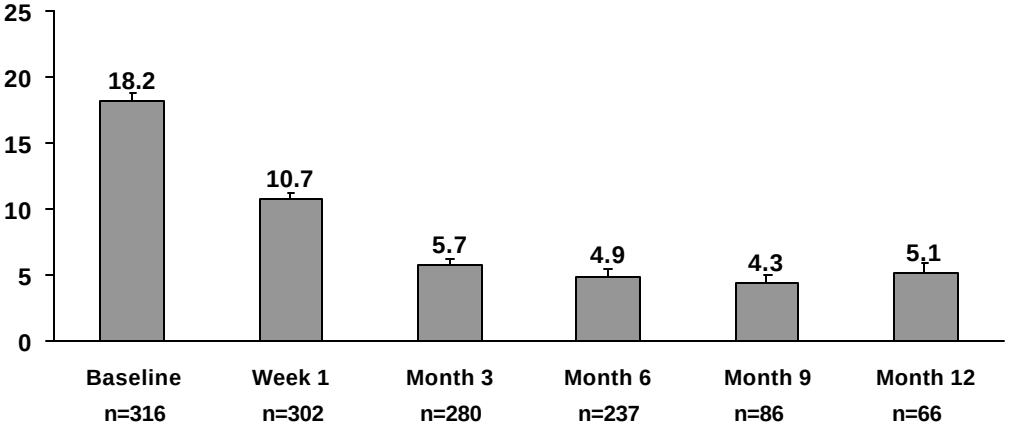
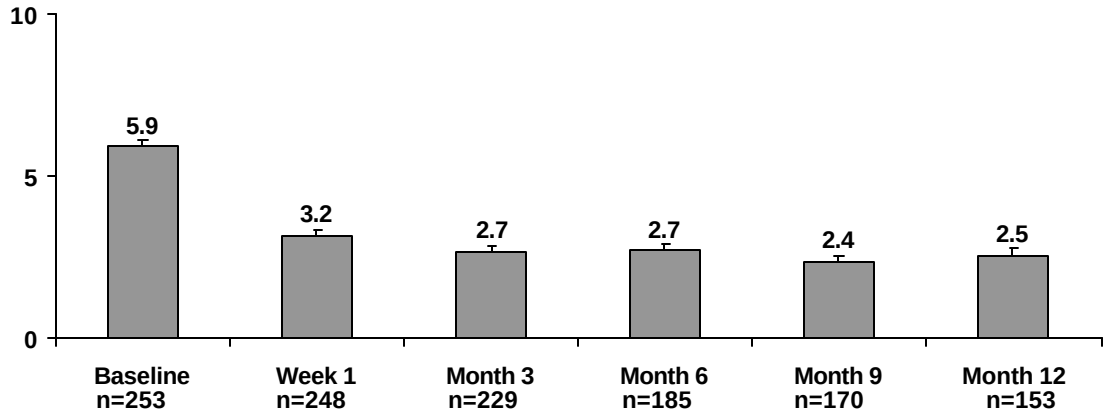


Figure 17: Pruritus Assessment By Visit: Long-Term Safety Studies

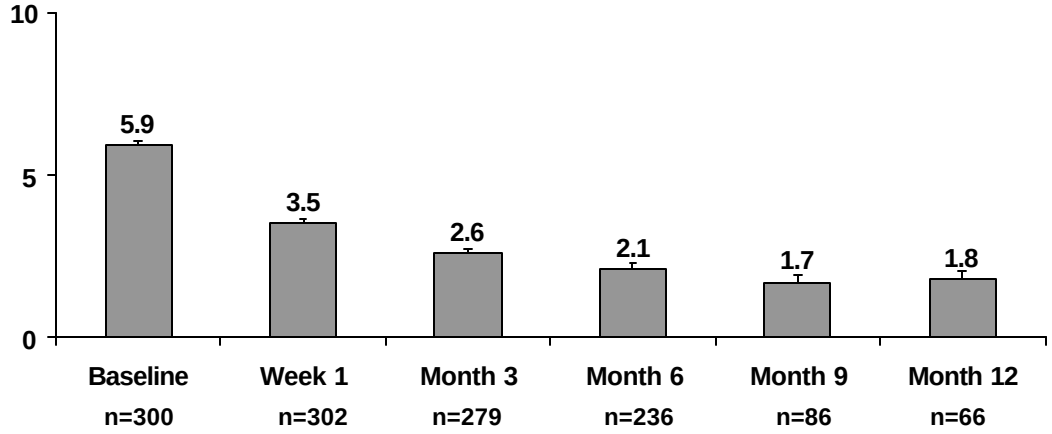
Pediatric Safety Study 96-0-025

Mean ±SE



Adult Safety Study FG-06-12

Mean ±SE



9 SAFETY

Safety was assessed in the five core studies based on adverse event and clinical laboratory data. The adverse events were coded using the same standardized COSTART dictionary.

A total of 1,554 patients were included in safety analyses; 983 in the three 12-week double blind studies and 571 in the two long-term studies

9.1 Three 12-Week, Double-Blind Studies

In the three 12-week, double-blind studies, a total of 64% of patients in the vehicle treatment group prematurely discontinued treatment, primarily due to lack of efficacy; this resulted in fewer treatment days for the vehicle group (median = 25.5 days) compared with the tacrolimus ointment treatment groups (median = 84 days, 0.03% and 85 days, 0.1%). Therefore, Kaplan-Meier analyses that adjusted for treatment days were performed. The adjusted incidence rate represents the expected incidence over 12 weeks. The adjusted incidence rate was the basis of statistical inferences with respect to the comparisons of adverse event incidence.

Since the pediatric population is of particular interest and the safety results for the adult population mirrored that for all patients, this briefing document will focus on all patients (adult and pediatric) and pediatric patients.

Notes to the reader

Regarding adverse events:

Note that since cultures were not performed, it is not clear if all folliculitis events represented bacterial folliculitis. Flu syndrome (flu-like symptoms) is a catch-all for a variety of events including cold, congestion, cold and congestion, cold symptoms, common cold, flu, head cold, influenza, upper respiratory infection, chest congestion, muscle ache secondary to cold, sinus cold, etc.

Regarding treatment difference figures in this safety section:

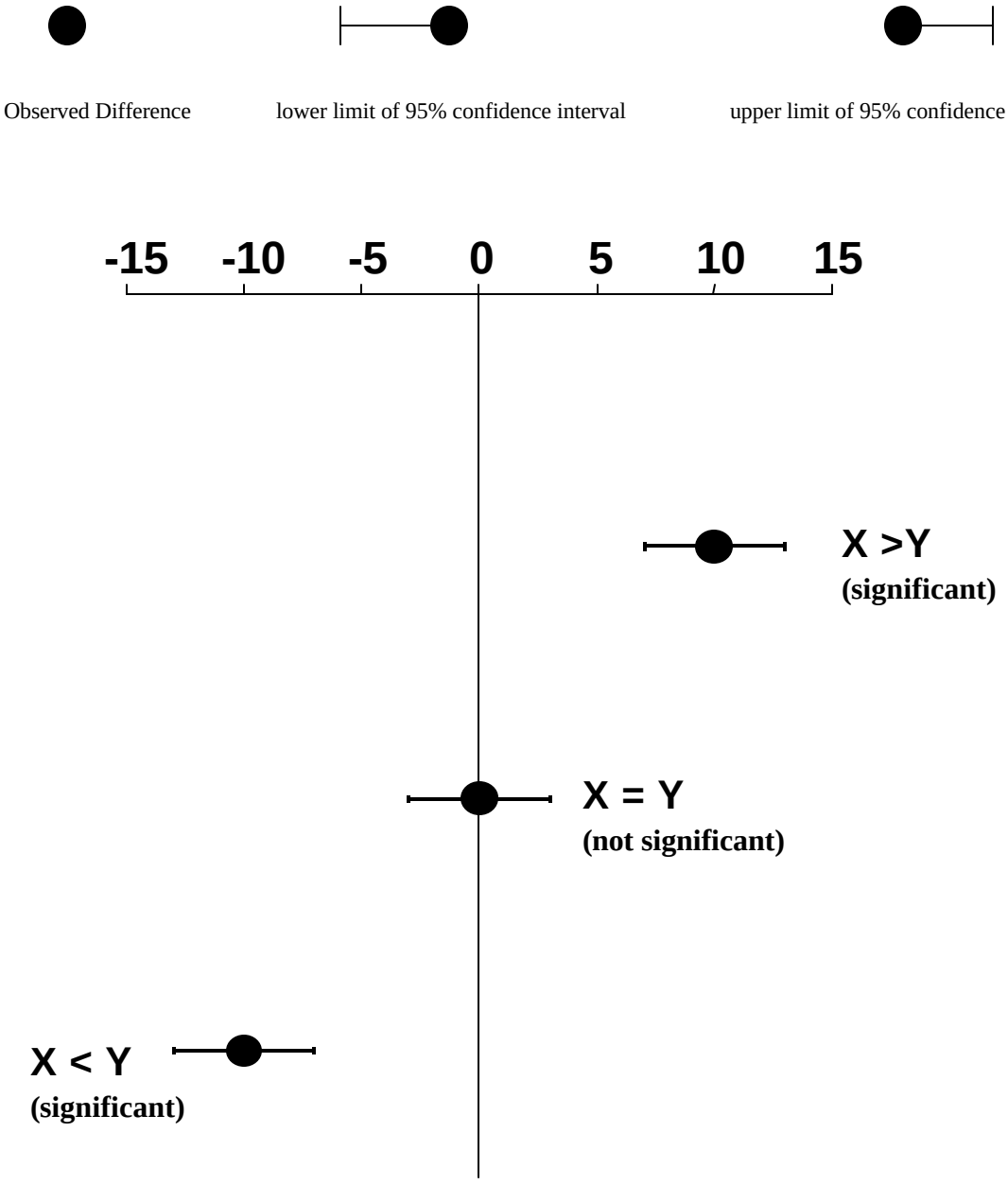
One way of presenting treatment differences in the incidence of events is to look at the 95% confidence intervals around the treatment difference. By plotting the confidence intervals, it is easy to graphically display the range of values (i.e., the upper and lower bounds of the interval) for the treatment difference within which one would expect (with 95% confidence) to find the "true" treatment difference.

Figure 18 illustrates the following outcomes.

- If the rate for treatment X is smaller than that for treatment Y (X<Y), then the treatment difference (X minus Y) is negative and would appear on the left side of the graph.
- If the rate for treatment X is larger than that for treatment Y (X>Y), then the treatment difference (X minus Y) is positive and would appear on the right side of the graph.
- If the rates for the two treatments are equivalent (X=Y), then the treatment difference (X-Y) is zero and would appear in the middle of the graph.

There is a close relationship between 95% confidence intervals (CI) and the result from a statistical test with a two-tailed significance level of 0.05. If the test result is significant ($p<0.05$), i.e., X and Y are different, the 95% CI for the treatment difference (X minus Y) does not cross the zero line. On the other hand, if the test is not significant ($p>0.05$), i.e., a difference between X and Y is not detected, the 95% CI for the difference (X minus Y) crosses the zero line. Thus, by plotting the confidence interval around the treatment difference, both the magnitude of the difference with its precision and the statistical significance of the difference are visually demonstrated. Treatment differences in the incidence of adverse events are presented in this fashion in this briefing document.

Figure 18: Example Treatment Difference With 95% Confidence Interval Plot



9.1.1 Adverse Events: All Patients

A summary of the adjusted 12-week incidence rates of adverse events occurring during the treatment period (treatment emergent) for the three 12-week, double-blind studies combined is presented in Table 22 and Figure 19, and, for adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle, in Table 23.

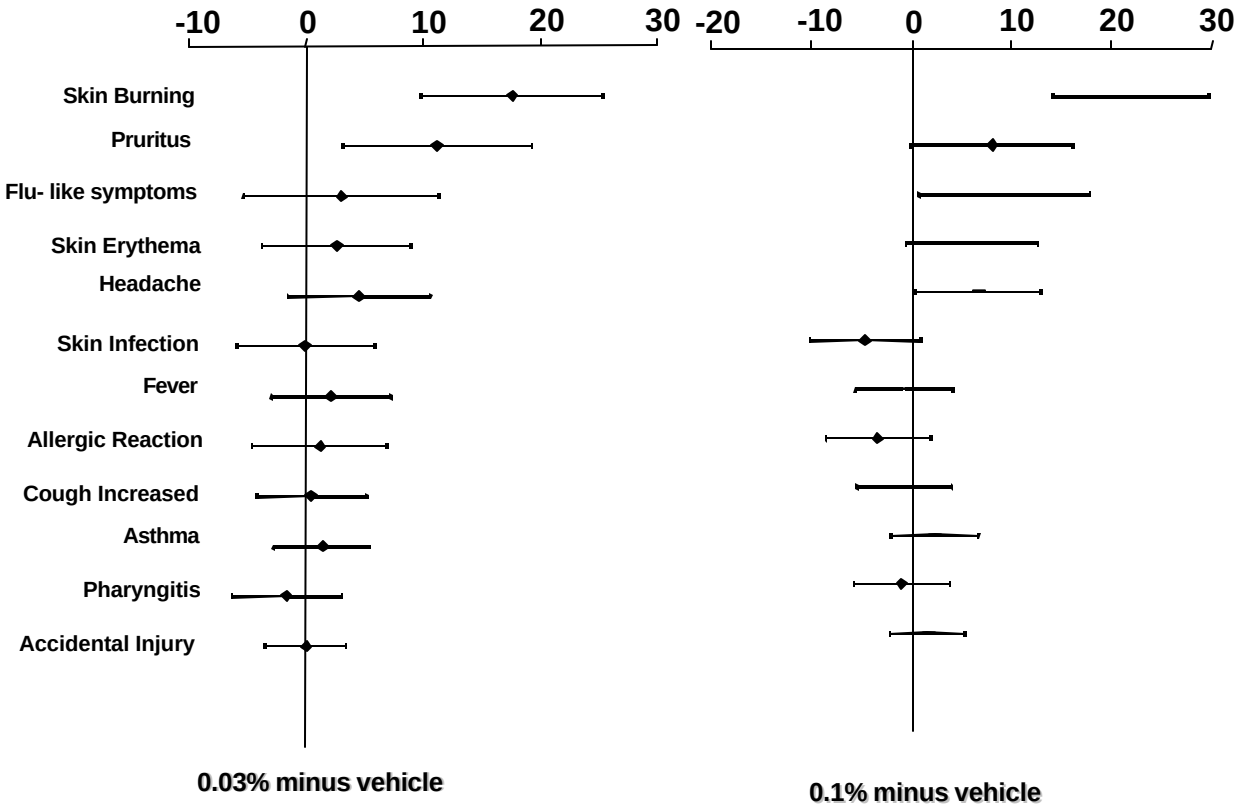
There were no statistically significant differences between either tacrolimus ointment concentration and vehicle with respect to overall adverse event incidence, the incidence of nonapplication site adverse events, or infections (Table 22). Fewer tacrolimus ointment-treated patients discontinued due to an adverse event compared with vehicle-treated patients (Table 22).

Table 22: Summary Of The Adjusted 12-Week Incidence Rate Of Treatment Emergent Adverse Events: Three 12-Week, Double-Blind Studies Combined

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle	0.03%	0.1%	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	N=328	N=328	N=327				
	Rate ± Standard Error‡						
Overall AE	83.9 ± 2.63	89.8 ± 1.79	88.5 ± 1.97	5.9 (-0.4, 12.1)	4.6 (-1.8, 11.1)	0.065	0.158
Overall Drug-Related AE	56.1 ± 3.08	72.4 ± 2.54	68.3 ± 2.66	16.4 (8.5, 24.2)	12.2 (4.2, 20.2)	<0.001	0.003
Application Site AE	59.5 ± 3.06	75.2 ± 2.47	72.4 ± 2.58	15.7 (8.0, 23.4)	12.8 (5.0, 20.6)	<0.001	0.001
Head/Neck AE‡‡	*(n=297)* 48.7 ±3.46	*(n=285)* 60.4 ±3.00	*(n=277)* 60.4 ±3.08	11.8 (2.8, 20.8)	11.7 (2.6, 20.8)	0.010	0.011
Non-Head/Neck AE	55.3 ±3.11	67.9 ± 2.65	67.5 ±2.69	12.7 (4.7, 20.7)	12.3 (4.2, 20.3)	0.002	0.003
Nonapplication Site AE	68.3 ± 3.74	69.7 ± 2.88	67.5 ± 2.89	1.4 (-7.9, 10.7)	-0.7 (-10.0, 8.5)	0.766	0.880
Infections	54.3 ± 3.91	56.4 ± 3.05	57.5 ± 3.13	2.1 (-7.6, 11.8)	3.2 (-6.6, 13.0)	0.670	0.522
AE Resulting in Discontinuation§§	*13.1 ±2.17*	*6.9 ±1.52*	*5.2 ±1.27*	*-6.2 (-11.4, -1.0)*	*-7.9 (-12.8, -3.0)*	*0.019*	*0.002*

Patient population: all randomized patients who received at least one dose of study drug.
CI: confidence interval. AE: adverse event.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Infections: a predefined cluster of events including such terms as flu syndrome, herpes simplex, chills and fever, etc. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
‡‡ Number (n) is equal to the number of patients applying study drug to the head/neck region.
§ From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05. *§§ Note the rate is highest in the vehicle group.*
Source: NDA 50-777 (Statistical Appendix 8.4.13.6.1.2.1).

Figure 19: Treatment Difference and 95% Confidence Intervals Around Treatment Difference for Common (³5% Incidence In Any Treatment Group) Adverse Events‡



‡ **Adjusted incidence rates based on Kaplan-Meier estimates at week 12.**

The left and right ends of the line represent the lower and upper 95% confidence limits (two-tailed) for the treatment difference. A line not crossing zero indicates a statistically significant ($p<0.05$) difference.

Table 23: Summary Of The Adjusted 12-Week Incidence Rate Of Individual Adverse Events†: Three 12-Week, Double-Blind Studies Combined

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

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval. † Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle. § From Normal Approximation test based on Kaplan-Meier estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12. Alcohol intolerance = skin/facial flushing, redness, heat sensation, etc. after alcohol consumption. Flu syndrome = flu-like symptoms; cold, common cold, influenza, upper respiratory infection, etc. Folliculitis = swollen or infected hair follicle. Hyperesthesia = generally localized, hypersensitive reaction, sensitive skin, skin sensitive to temperature changes, etc. Skin burning = burning sensation, pain, stinging, soreness, etc.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: NDA 50-777 (Statistical Appendix 8.4.13.6.1.2.2).

The adverse events associated with the application of tacrolimus ointment were generally limited to local irritation (e.g., pruritus, the sensation of skin burning). More tacrolimus ointment-treated patients with severe atopic dermatitis at baseline, or with >75% of their body surface area affected at baseline, tended to experience the sensation of burning than did those with moderate disease or smaller affected body surface areas. However skin burning and other local irritation events were of short duration, occurred early in treatment (generally during the first few days of treatment before skin condition improved, Figure 20) and rarely required discontinuation of treatment (tacrolimus ointment-treated patients: <2% pediatric patients; <5% adults).

Based on the results of the three 12-week, double-blind studies, patients applying tacrolimus ointment also had a higher adjusted incidence rate compared with vehicle for such events as flu syndrome (*flu-like symptoms*), headache, acne, folliculitis, alcohol intolerance (*skin/facial flushing, redness, heat sensation, etc. after alcohol consumption*), hyperesthesia (*generally localized, sensitive skin, skin sensitive to temperature changes, etc.*), skin tingling, dyspepsia *(upset stomach, indigestion*), herpes zoster (*5 of 6 cases were chicken po*x), cyst, and myalgia.

Although higher than vehicle, the incidence of headache was still in the range of what one might expect in the general population. For example, headache rates of 12% and 24% have been reported in the United States [1]; the incidence in the 12-week, double-blind studies in the 0.1% tacrolimus ointment group was 16% for all patients and 19% for adults. In addition, the flu-like symptoms reported in these studies may not be viral infection. Dyspepsia generally was upset stomach or indigestion. Acne as reported in these studies may be more of a sterile folliculitis secondary to the occlusive nature of the ointment vehicle as opposed to a true acne vulgaris. Skin tingling and hyperesthesia (*generally localized, hypersensitive to temperature, sensitive skin, etc.*) may also be to

some extent a reflection of the local action of tacrolimus ointment. These events are reversible upon discontinuation of tacrolimus ointment.

Application of either concentration of tacrolimus ointment to the head and neck (thin skin areas) did not result in a higher incidence of application site adverse events than application to other regions of the body.

It is noteworthy that only 5% of tacrolimus ointment-treated patients discontinued treatment due to an adverse event (i.e., the perceived clinical response did not outweigh the adverse event experience). In these studies, a statistically significantly higher percentage of vehicle-treated patients (11%) discontinued due to an adverse event than tacrolimus ointment-treated patients.

There were no patient deaths in these studies. The incidence of serious adverse events during treatment was similar for vehicle-treated (1.5%) and tacrolimus ointment-treated (1.7%) patients. Of these serious treatment emergent adverse events, only one event in a pediatric patient and one event in an adult patient was considered by the investigator to have a possible relationship to tacrolimus ointment. Patient No. 216754 (0.1% tacrolimus ointment), a 12-year old male of mixed race with severe atopic dermatitis experienced mild skin erythema on the forehead on study days 5 and 6. The patient stopped treating the forehead area, but continued treating the remainder of affected body surface area. The event was considered to be of medical importance since the patient was seen in the emergency room and was given diphenhydramine hydrochloride (Benadryl®). The patient recovered with no sequelae, resumed treatment to the forehead, had no further episodes of erythema, and completed the study.

Patient No.198534 (0.1% tacrolimus ointment), a 25-year-old African American female, had "leukopenia" reported on Day 8 based on a reduction in neutrophil and white blood cell (WBC) counts. Study drug was interrupted from Day 9-19 and permanently discontinued on Day 23. The patient was subsequently diagnosed with benign neutropenia of African Americans by an outside consultant. After reviewing the patient's past medical history and current medications, the independent consultant concluded that the variations observed in her absolute neutrophil count were not inconsistent with the known patterns of this syndrome. He also postulated that the patient's atopic dermatitis may have artificially increased her neutrophil counts which returned to her normal low level as her inflammation decreased with tacrolimus ointment treatment. Neutrophil and WBC values for this patient were as follows (L=value below normal range):

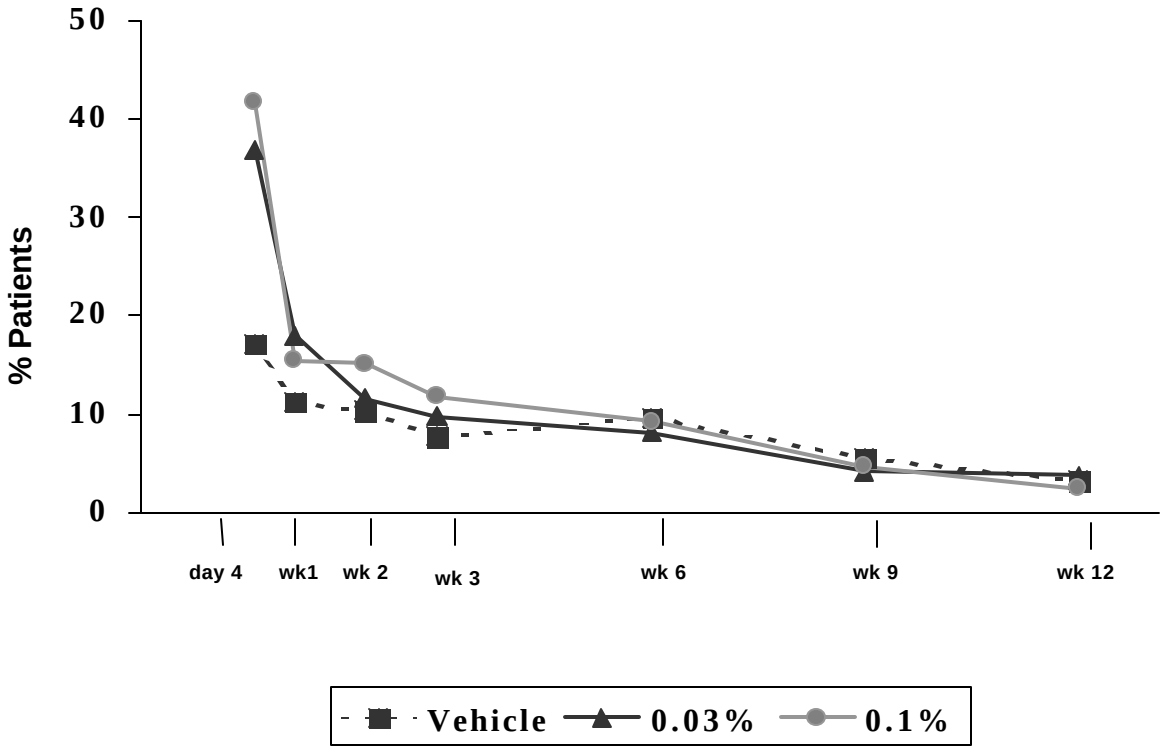
Day	Neutrophils (%)	WBC ($x10^9$/L)
Baseline	58.8	3.4L
8	36.4L	2.2L
15	63.3L	3.0L
22	25.0L	2.0L
29†	42.9L	2.1L
44†	33.3L	2.1L

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

Note that the WBC count was below the lower limit of normal at baseline and the neutrophil and WBC counts fluctuated below the lower limit of the normal range both during treatment and posttreatment, consistent with a diagnosis of benign neutropenia of African Americans.

In the three 12-week, double-blind studies, no consistent changes or notable differences among treatment groups in laboratory profile were observed (see also Section 9.6).

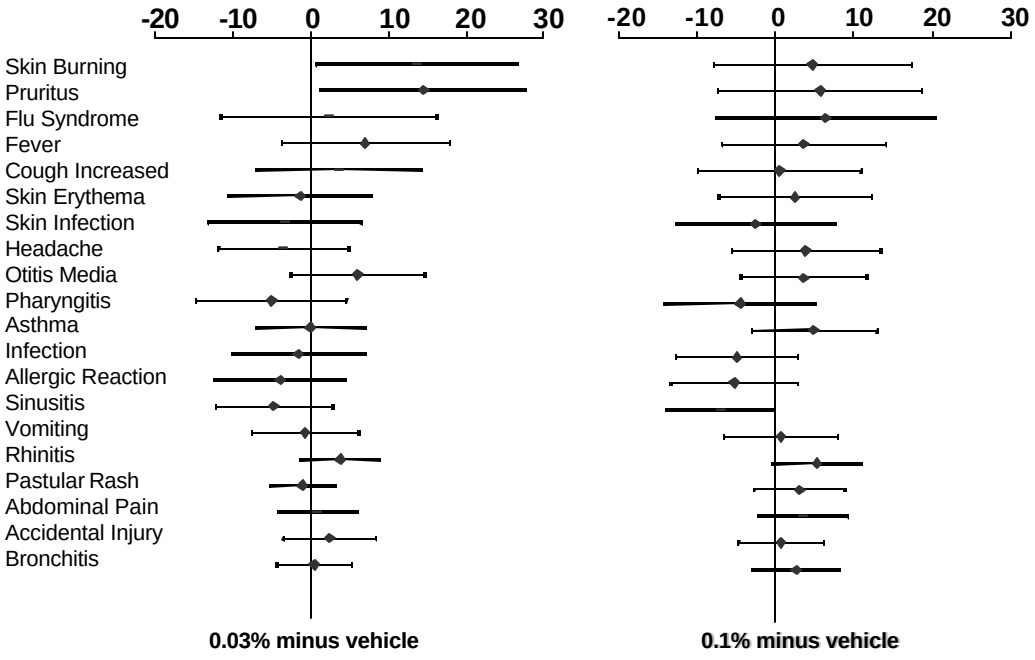
Figure 20: Prevalence of The Application Site Adverse Event Skin Burning



9.1.2 Adverse Events: Pediatric Patients

Treatment group differences in the incidence of common adverse events (incidence of at least 5% in any treatment group) in pediatric patients are summarized in Figure 21.

Figure 21: Common Adverse Events in Pediatric Patients
Treatment Group Differences with 95% Confidence Intervals



The left and right ends of the line represent the lower and upper 95% confidence limits (two-tailed) for the treatment difference. A line not crossing zero indicates a statistically significant ($p<0.05$) difference. Common=incidence of at least 5% in any treatment group.

A summary of the adjusted 12-week incidence rates of adverse events in pediatric patients that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle is presented in Table 24.

Table 24: Summary Of The Adjusted 12-Week Incidence Rate Of Individual Adverse Events†: Pediatric Patients (2-15 Years Of Age) In The Three 12-Week, Double-Blind Studies

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

Patient population: all randomized patients who received at least one dose of study drug. CI: confidence interval.
Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age; this patient is categorized by true age and included in the pediatric analyses.
† Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle.
§ From Normal Approximation test based on Kaplan-Meier Estimates. Statistical significance is indicated by p-values ≤0.05.
‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
Skin burning = burning sensation, pain, stinging, soreness, etc.
Herpes zoster = five cases of *chicken pox*.
§§ Note that the rate is highest in the vehicle group.
Source: NDA 50-777 (Statistical Appendix 8.4.13.6.1.2.3).

For pediatric patients in the 0.1% tacrolimus ointment group, no adverse event had a statistically greater adjusted 12-week incidence rate compared with vehicle. The adjusted incidence rate of sinusitis was higher in the vehicle group compared with the 0.1% tacrolimus ointment group. Herpes zoster was the only infection with a statistically greater adjusted incidence rate in the 0.03% tacrolimus ointment group compared with vehicle; the events were five cases of *chicken pox*. The patients with chicken pox had a normal clinical course as related by the managing physician and all recovered without sequelae. Since no statistically significant difference was observed in the 0.1% tacrolimus ointment treatment group compared with vehicle, it is likely that the five cases were by chance in an *at risk* patient population (i.e., school age children) rather than drug -related events.

The results were similar for young pediatric patients 2 to 6 years of age (Table 25).

Table 25: Summary of the Adjusted 12-Week Incidence Rate of Individual Adverse Events†: Young Pediatric Patients (2-6 Years of Age)

COSTART Term	Treatment Group			Treatment Difference (95% CI)		p-Value§	
	Vehicle	0.03%	0.1%	0.03% minus Vehicle	0.1% minus Vehicle	0.03% vs Vehicle	0.1% vs Vehicle
	n=72	n=74	n=69				
	Rate ± Standard Error‡						
Herpes Zoster (chicken pox)	0.0 ± 0.00	7.8 ± 3.79	0.0 ± 0.00	7.8 (0.4, 15.2)	0 (0, 0)	0.040	na
Pruritus	26.6 ± 6.17	47.2 ± 5.94	28.3 ± 5.53	20.6 (3.8, 37.4)	1.7 (-14.5, 18.0)	0.016	0.837
Sinusitis§§	*12.6 ±5.03*	*3.5 ±2.46*	*1.8 ±1.77*	*-9.0 (-20.0, 1.9)*	*-10.8 (-21.3, -0.4)*	*0.106*	*0.043*

Patient population: all randomized patients 2 to 6 years of age who received at least one dose of study drug. CI: confidence interval. † Includes adverse events that had a statistically significant difference between either tacrolimus ointment treatment group and vehicle.
§ From Normal Approximation test based on Kaplan-Meier Estimates. Statistical significance is indicated by p-values ≤0.05. ‡ Adjusted rates are based on Kaplan-Meier estimates at Week 12.
§§ Note that the rate is highest in the vehicle group.
Source: data included in NDA 50-777.

In general, the overall incidence of adverse events was generally somewhat higher among younger children (2-6 years of age) than older children (7-15 years of age) in all three treatment groups (vehicle and tacrolimus ointment groups). Younger children tended to have a higher incidence of flu-like symptoms, increased cough, fever and otitis media compared with older children in all three treatment groups (vehicle and tacrolimus ointment groups). This is not unexpected given that this age group is undergoing *first exposure* to other children. Also, it is known that children under the age of 7 years experience more otitis media than either older children or adults due to their shorter, wider, more horizontal eustachian tubes which have a decreased stiffness of supporting cartilage and a smaller drainage orifice [9, 10, 11]. Children with atopic diseases have been reported to have a predisposition to otitis media [12, 13].

Since age differences in the incidence of individual adverse events were observed in all treatment groups, including vehicle, tacrolimus ointment does not appear to be associated with any age-related/selective effect. Young children (2 to 6 years of age) are not at a higher risk for adverse events compared with older children or adults.

9.1.3 Adverse Events Leading to Discontinuation

The incidence of the more common adverse events leading to discontinuation in the three pivotal studies is summarized by age in Table 26, with all adverse events leading to discontinuation listed in Table 27.

Table 26: Summary of the Incidence of Common Adverse Events† Leading to Discontinuation By Age: Three 12-Week, Double-Blind Studies

		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Pediatric Patients (2-15 years of age)‡		***n=116***	***n=118***	***n=118***
Any Adverse Event		9 (7.8%)	6 (5.1%)	3 (2.5%)
Skin & Appendages	Pruritus	2 (1.7%)	2 (1.7%)	0
	Skin Erythema	2 (1.7%)	1 (0.8%)	0
	Skin Burning	2 (1.7%)	1 (0.8%)	0
	Skin Infection	2 (1.7%)	0	0
2-6 years of age		*n=72*	*n=74*	*n=69*
Any Adverse Event		5 (6.9%)	6 (8.1%)	1 (1.4%)
Skin & Appendages	Pruritus	1 (1.4%)	2 (2.7%)	0
	Skin Erythema	2 (2.8%)	1 (1.4%)	0
	Skin Burning	2 (2.8%)	1 (1.4%)	0
	Skin Infection	0	0	0
7-15 years of age‡		*n=44*	*n=44*	*n=49*
Any Adverse Event		4 (9.1%)	0	2 (4.1%)
Skin & Appendages	Pruritus	1 (2.3%)	0	0
	Skin Erythema	0	0	0
	Skin Burning	0	0	0
	Skin Infection	2 (4.5%)	0	0
Adult Patients (³16 years of age)		***n=212***	***n=210***	***n=209***
Any Adverse Event		26 (12.3%)	13 (6.2%)	11 (5.3%)
Skin & Appendages	Pruritus	17 (8.0%)	7 (3.3%)	6 (2.9%)
	Skin Erythema	10 (4.7%)	1 (0.5%)	1 (0.5%)
	Skin Burning	6 (2.8%)	6 (2.9%)	7 (3.3%)
	Skin Infection	3 (1.4%)	0	0

Patient population: all randomized patients who received at least one dose of study drug.
† Experienced by at least 1% of patients in any treatment group regardless of age. A patient could have discontinued for more than one adverse event.
‡ Patient No. 84515 was enrolled in adult Study 97-0-035 despite being 15 years of age. In this table, this patient is categorized by true age.
Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult).
Source: NDA 50-777 (Statistical Appendix 8.4.13.6.7.2).

Table 27: Summary of the Adverse Events Leading to Discontinuation in Each of the Three 12-Week, Double-Blind Studies

Group	Patient No.	Age (yrs)	COSTART Term	Application Site (Yes/No)	Relationship Yes/No)§	Adverse Event Days (onset/end)	Out-come	Last Dose Day
97-0-035								
Vehicle	19518	32	Pruritus	Yes	Yes	1/7	R	7
			Skin Erythema	Yes	Yes	1/7	R	
	83502	20	Skin Infection	Yes	Yes	79/87	R	81
	156503	53	Skin Erythema	Yes	Yes	1/4	R	3
			Edema	Yes	Yes	2/3	R	
			Pruritus	Yes	Yes	2/3	R	
	158504	44	Pruritus	No	Yes	8/-	P	14
	164505	28	Pruritus	Yes	Yes	1/9	R	6
			Skin Erythema	Yes	Yes	2/17	RS	
			Skin Burning	Yes	Yes	2/7	R	
	164506	51	Pruritus	Yes	Yes	2/9	R	6
	198511	36	Allergic Reaction	No	No	42/44	R	44
	198522	27	Pruritus	Yes	Yes	8/36	R	12
			Skin Burning	Yes	Yes	8/36	R	
	198528	49	Pruritus	Yes	Yes	2/7	R	6
			Skin Erythema	Yes	Yes	2/7	R	
	198531	25	Hyperesthesia	Yes	Yes	1/10	R	8
			Maculopapular Rash	Yes	Yes	1/10	R	
	198536	26	Leukopenia	No	Yes	11/35	R	21
	233501	56	Skin Infection	Yes	No	16/36	R	22
0.03%	19504	38	Asthma	No	No	43/50	R	43
	155504	65	Skin Burning	Yes	Yes	1/1	R	1
	198537	56	Pruritus	Yes	Yes	1/5	R	5
	236510	46	Acne	Yes	Yes	9/49	R	30
			Skin Burning	Yes	Yes	21/33	R	
			Pruritus	Yes	Yes	1/29	R	
	237512	30	Photosensitivity Reaction	No	No	71/84	R	72
0.1%	11506	50	Skin Burning	Yes	Yes	8/-	P	8
	11508	32	Skin Burning	Yes	Yes	1/4	R	2
	23507	50	Exacerbation of Untreated Area	No	No	19/20	R	21
	84511	26	Eczema	Yes	Yes	1/5	R	1
			Skin Burning	Yes	Yes	1/2	R	
			Skin Erythema	Yes	Yes	1/5	R	
	198533	61	Skin Burning	Yes	Yes	2/2	R	2
			Pruritus	Yes	Yes	2/2	R	
	198534	25	Leukopenia [subsequent diagnosis of benign neutropenia of African Americans]	No	Yes [subsequently changed to unlikely]	22/-	P	23
	236507	71	Pruritus	Yes	Yes	1/7	R	8

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(Table 27 continued)

Group	Patient No.	Age (yrs)	COSTART Term	Application Site (Yes/No)	Relationship (Yes/No)§	Adverse Event Days (onset/end)	Out-come	Last Dose Day
97-0-036								
Vehicle	14617	34	Angioedema	Yes	Yes	3/20	R	17
			Face Edema	Yes	Yes	3/20	R	
	85602	29	Skin Erythema	Yes	Yes	3/7	R	5
			Skin Burning	Yes	Yes	2/7	R	
			Pruritus	Yes	Yes	2/7	R	
	154601	33	Pustular Rash	Yes	Yes	1/8	R	8
			Skin Burning	Yes	Yes	1/8	R	
			Skin Erythema	Yes	Yes	1/8	R	
			Fever	No	Yes	7/8	R	
			Arthralgia	No	Yes	7/8	R	
			Exfoliative Dermatitis	Yes	Yes	7/8	R	
	154612	17	Pruritus	Yes	Yes	2/4	R	4
			Skin Erythema	Yes	Yes	2/4	R	
	173603	42	Sweating	Yes	Yes	1/3	R	2
			Pruritus	Yes	Yes	1/3	R	
	216611	55	Pruritus	Yes	Yes	3/7	R	6
	216613	51	Skin Infection	Yes	No	12/17	R	16
	217603	32	Pruritus	Yes	Yes	5/14	R	7
			Dry Skin	Yes	Yes	5/14	R	
	221609	43	Pruritus	Yes	Yes	1/9	R	7
	221614	34	Skin Erythema	Yes	Yes	1/2	R	2
			Skin Burning	Yes	Yes	1/2	R	
			Pruritus	Yes	Yes	1/2	R	
	231616	59	Pruritus	Yes	Yes	1/1	R	1
			Skin Erythema	Yes	Yes	1/1	R	
	231617	63	Urticaria	Yes	Yes	3/4	R	3
	245611	40	Pruritus	Yes	Yes	1/6	R	1
			Skin Burning	Yes	Yes	1/6	R	
	245615	33	Dry Skin	Yes	Yes	3/-	P	4
			Rash	No	Yes	3/23	R	
			Pruritus	No	Yes	3/23	R	
			Pruritus	Yes	Yes	3/-	P	
			Skin Erythema	Yes	Yes	3/-	P	
			Skin Disorder	No	Yes	3/23	R	
0.03%	14601	31	Pruritus	Yes	Yes	15/18	R	18
			Skin Burning	Yes	Yes	15/20	R	
	14607	42	Pruritus	Yes	Yes	1/2	R	2
			Skin Burning	Yes	Yes	1/2	R	
	14618	56	Herpes Simplex	Yes	Yes	41/64	R	41
	44604	47	Pruritus	Yes	Yes	1/11	R	7
			Skin Erythema	Yes	Yes	1/11	R	
	85601	47	Pruritus	Yes	Yes	2/47	R	46
	107612	50	Skin Burning	Yes	Yes	1/7	R	7
	160616	75	Maculopapular Rash	Yes	Yes	4/14	R	8
			Maculopapular Rash	Yes	Yes	4/17	R	

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(Table 27 continued)

Group	Patient No.	Age (yrs)	COSTART Term	Application Site (Yes/No)	Relationship (Yes/No)§	Adverse Event Days (onset/end)	Out-come	Last Dose Day
0.03%	216614	49	Skin Burning	Yes	Yes	1/2	R	2
			Pruritus	Yes	Yes	1/2	R	
0.1%	221602	40	Skin Burning	Yes	Yes	14/-	P	15
			Pruritus	Yes	Yes	9/-	P	
	14623	47	Pruritus	Yes	Yes	1/1	R	1
			Pruritus	Yes	Yes	1/2	R	
			Skin Burning	Yes	Yes	1/2	R	
			Skin Burning	Yes	Yes	1/1	R	
	231627	50	Pruritus	Yes	Yes	1/3	R	2
			Edema	Yes	Yes	1/2	R	
			Skin Burning	Yes	Yes	1/ 2	R	
			Skin Burning	Yes	Yes	2/5	R	
			Exfoliative Dermatitis	Yes	Yes	2/8	R	
	232607	73	Pruritus	Yes	Yes	15/-	P	43
			Alopecia	No	No	21/113	R	
97-0-037								
Vehicle	89751	12	Folliculitis	Yes	Yes	58/78	R	57
	154702	3	Skin Erythema	Yes	Yes	1/3	R	3
			Skin Burning	Yes	Yes	1/3	R	
	154754	11	Skin Infection	Yes	Yes	8/-	P	22
	158702	3	Skin Erythema	Yes	Yes	5/11	R	4
	195705	4	Pustular Rash	Yes	Yes	2/24	R	15
	215751	10	Skin Infection	Yes	Yes	57/83	R	73
	221714	4	Skin Burning	Yes	Yes	1/4	R	3
			Pruritus	Yes	Yes	1/4	R	
	225751	10	Pruritus	Yes	Yes	1/3	R	2
	245703	4	Pustular Rash	Yes	Yes	8/13	R	12
			Fever	No	Yes	8/11	R	
0.03%	154713	5	Herpes Zoster	No	No	87/94	R	87
	158701	3	Asthma	No	No	41/46	R	41
	195703	2	Skin Erythema	Yes	Yes	1/2	R	1
			Pruritus	Yes	Yes	1/2	R	
	220711	2	Herpes Zoster	No	No	50/67	R	50
	236706	2	Pruritus	Yes	Yes	1/20	R	8
			Skin Burning	Yes	Yes	1/20	R	
	245704	3	Herpes Zoster	No	No	82/91	R	82

Table continued on next page

(Table 27 continued)

Group	Patient No.	Age (yrs)	COSTART Term	Application Site (Yes/No)	Relationship (Yes/No)§	Adverse Event Days (onset/end)	Out-come	Last Dose Day
0.1%	89703	6	Asthma	No	No	3/17	R	8
	153752	8	Urticaria	Yes	No	23/28	R	23
	154752	8	Skin Disorder	Yes	Yes	15/71	R	41

Patient population: Intent-to-treat ; all randomized patients who were dispensed and received at least one dose of study drug. Four patients in the adult studies (one in the vehicle treatment group, one in the 0.03% tacrolimus ointment treatment group and two in the 0.1% tacrolimus ointment treatment group) discontinued due to pregnancy; pregnancy was recorded as an adverse event due to Fujisawa Healthcare, Inc. administrative convention. These patients are not included as having discontinued due to an adverse event in this table. Skin burning = burning sensation, pain, stinging, soreness, etc.R=recovered, no residual effect. P=persistent condition. RS=recovered, with sequelae § yes=possible or probable, no=none. Studies 97-0-037 (Pediatric), 97-0-035 (Adult), and 97-0-036 (Adult). Source: NDA 50-777 (Study Reports R98-0214-506-C3-E, 1999000006, and 1999000008; Listing 14.4.4.1)

Very few non-skin adverse events led to discontinuation in both pediatric and adult patients.

9.2 Comparison of 0.1% versus 0.03% Tacrolimus Ointment: Safety

In the 12-week, double-blind studies, adverse events with a statistically significantly higher 12-week adjusted incidence in the 0.1% tacrolimus ointment group compared with vehicle (but not in the 0.03% tacrolimus ointment group compared with vehicle) included flu syndrome, headache, acne, cyst, dyspepsia, skin tingling, and hyperesthesia (generally localized sensitivity, for example to temperature).

No adverse event had a statistically significantly higher incidence in the 0.1% tacrolimus ointment group compared with the 0.03% tacrolimus ointment group.

In pediatric patients in these studies, no adverse event had a statistically greater 12-week adjusted incidence in the 0.1% tacrolimus ointment group compared with vehicle. Four

events had a statistically higher incidence in the 0.03% tacrolimus group compared with vehicle; these were skin burning, pruritus, chicken pox (COSTART herpes zoster) and small blisters (COSTART vesiculobullous rash).

9.3 Two Long-Term Safety Studies

The two long-term studies were designed so that the enrollment numbers would fulfill the ICH guidelines for long-term exposure studies. Of the 571 patients included in the safety analyses, 81.4% (465) had at least 6 months on study and 43.4% (248) had at least 12 months on study. Of the 255 pediatric patients in this long-term safety study population, 219 (85.9%) had at least 6 months on study; 180 patients (70.6%) had at least 12 months on study. The incidence of adverse events in the long-term studies is summarized in Table 28. [Hazard rates for adverse events of patients applying 0.1% tacrolimus ointment in all five studies are presented in Section 9.5.]

9.3.1 Adverse Events

Table 28: Summary Of The Raw Incidence Of Adverse Events: Long-Term Studies

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

† All enrolled patients who received at least one dose of study drug.
‡ All enrolled patients who received at least one dose of study drug and had postbaseline data. Drug-related: possibly or probably related to study drug, assessment missing, or not assessable based on the investigator's assessment. § Based on an *infection cluster* of COSTART terms (e.g., flu syndrome, herpes simplex, chills and fever, etc.). Source: NDA 50-777 (Study Reports R98-0213-506-C3-E and FG98-506-07).

No safety concerns with long-term use were identified in these studies. As in the shorter-term studies (≤12 weeks), the majority of adverse events associated with long-term use of 0.1% tacrolimus ointment were local irritation events of mild or moderate severity and limited duration which generally occurred early in treatment.

The most common application site adverse events were the sensation of skin burning and pruritus (Table 29 and Table 30). Skin infection was also relatively common; however,

this likely reflects the natural history of moderate to severe atopic dermatitis and/or the occlusive nature of the vehicle. Even so, the incidence was somewhat lower than one might expect in an atopic dermatitis population over the course of a year based on reports in the literature [2].

Table 29: Incidence And Severity Of Common Application Site Adverse Events In Long-Term Pediatric Safety Study 96-0-025

Body System COSTART Term	Incidence n=255	Severity+		
		Mild	Moderate	Severe
Any application site adverse event	138(54.1%)	44	71	23
Skin and Appendages				
Skin burning	66(25.9%)	30	28	8
Pruritus	59(23.1%)	16	35	8
Skin infection	29(11.4%)	7	16	6
Skin erythema	23 (9.0%)	12	9	2

Patient population: all enrolled patients who received at least one dose of study drug.
Common: experienced by at least 5% of patients.
+ Severity was based on the most severe episode.
Source: NDA 50-777 (Study Report R98-0213-506-C3-E, Tables 13.5.3.1 and 13.5.3.3).

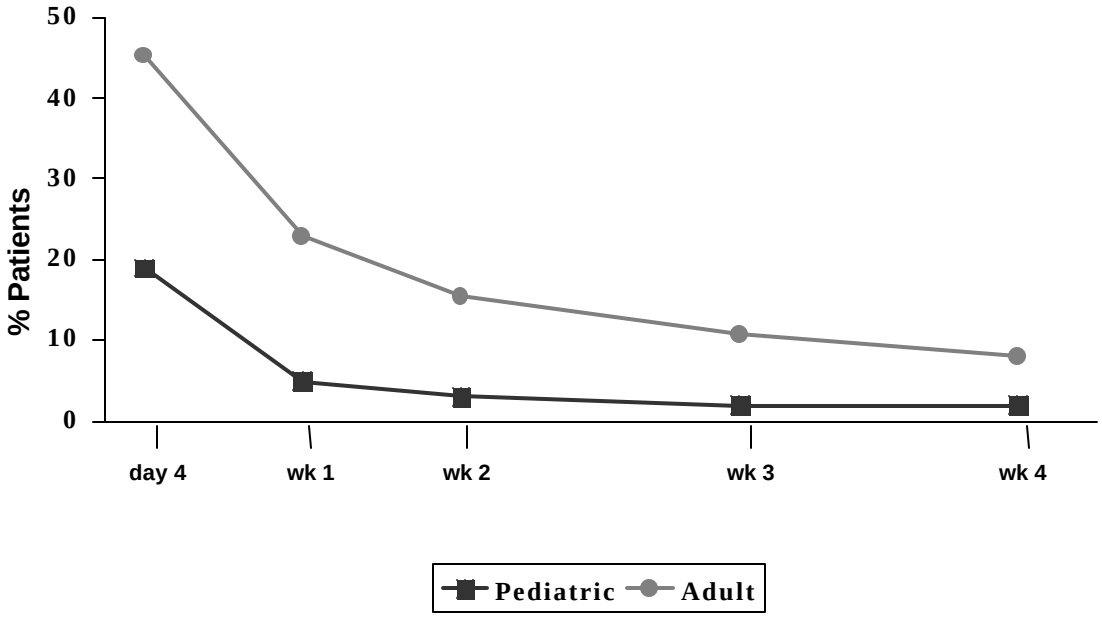
Table 30: Incidence And Severity Rating Of Most Frequently Reported Application Site Adverse Events† In Long-Term Adult Study FG-06-12

	Patients (n=316)	%	Severity §		
			mild	moderate	severe
Skin and appendages					
Skin burning	148	46.8	46	57	45
Pruritus	75	23.7	17	24	34
Skin erythema	38	12.0	14	20	4
Skin infection	35	11.1	18	10	7
Folliculitis	28	8.9	20	5	3
Herpes Simplex	24	7.6	8	12	4
Body as a whole					
Lack of drug effect	30	9.5	5	17	8
Alcohol intolerance	15	4.7	9	3	3

†Application-site adverse events with an incidence of at least 15 patients (4.7% of total study population)
§ The worst episode per patient was used for the analysis of severity
Source: NDA 50-777 (Study Report FG98-506-07, Table 13.5.2.1).

The prevalence of application site adverse events (e.g., the sensation of skin burning, pruritus) tended to decrease after the first few days of treatment, presumably as disease status improved in both the long-term pediatric and adult studies (Figure 22).

Figure 22: Prevalence Of Skin Burning In The Long-Term Safety Studies



The incidence of nonapplication site adverse events is summarized in Table 31. [Hazard rates for adverse events of patients applying 0.1% tacrolimus ointment in all five studies are presented in Section 9.5.]

Table 31: Incidence Of Common Nonapplication Site Adverse Events In Long-Term Pediatric (Study 96-0-025) And Adult (FG-06-12) Safety Studies

Body System **COSTART Term**	**Pediatric Study** n=255		**Adult Study** n=316	
Body as a Whole				
Flu syndrome	88	(34.5%)	69	(21.8%)
Fever	45	(17.6%)	5	(1.6%)
Allergic reaction	39	(15.3%)	66	(20.9%)
Accidental injury	27	(10.6%)	12	(3.8%)
Infection	20	(7.8%)	45	(14.2%)
Abdominal pain	13	(5.1%)	4	(1.3%)
Respiratory System				
Asthma	41	(16.1%)	15	(4.7%)
Cough increased	37	(14.5%)	9	(2.8%)
Pharyngitis	25	(9.8%)	15	(4.7%)
Rhinitis	12	(4.7%)	15	(4.7%)
Sinusitis	17	(6.7%)	9	(2.8%)
Bronchitis	15	(5.9%)	10	(3.2%)
Digestive System				
Diarrhea	15	(5.9%)	12	(3.8%)
Vomiting	13	(5.1%)	2	(0.6%)
Nervous System				
Headache	46	(18.0%)	32	(10.1%)
Skin and Appendages				
Herpes Simplex	11	(4.3%)	20	(6.3%)
Special Senses				
Otitis media	17	(6.7%)	4	(1.3%)

Patient population: all enrolled patients who received at least one dose of study drug.
Common: experienced by at least 5% of patients in pediatric Study 96-0-025 or 15 patients (4.7%) in adult Study FG-06-12.
Source: NDA-50-777 (Tables 13.5.6.1 and 13.5.6.3).

The incidence of nonapplication site adverse events, including those related to the gastrointestinal system, the nervous system (e.g., headache), and infections did not increase with increasing duration of study drug exposure or cumulative ointment use.

Except for flu-like symptoms, which showed (as might be expected) an apparent seasonal effect, there was no marked increase or decrease in the prevalence of any nonapplication site adverse event over time. Even if all the flu-like symptoms events reflected a true flu rather than a catch-all (e.g., cold, congestion, cold and congestion, cold symptoms, common cold, flu, head cold, influenza, upper respiratory infection, chest congestion, muscle ache secondary to cold, sinus cold, etc.), the rate is within that expected for the general population [8]. For example, according to the Center for Disease Control, the prevalence of flu syndrome in the United States in 1994 was 35% for the general population (37% under age 5 years, 46% for ages 5-17 years, ~38% for ages 18 to 44 years, and 26% for ages 45-64 years) [8]. For the long-term safety studies, flu-like symptoms were reported for 34% of pediatric patients and 22% of adult patients and was seasonally-related.

Given that *difficult to manage* atopic dermatitis patients had a substantial representation in the long-term core studies (>50% of patients had severe disease, generally disease present for most of the patient's life, most patients had approximately one-third of the BSA affected by disease, most patients [88%] had facial/neck lesions), the incidence of infection observed in these studies was not only relatively low but less than might be anticipated given the protocol-defined restrictions on the use of prophylactic antibiotics which are frequently included in multi-agent regimens used to treat such patients with severe or otherwise difficult to manage disease by most managing physicians.

For example, in one prospective study of 190 children with atopic dermatitis studied over a 2.5 year period (mean observation period of 13 months), 76 (40%) had 164 episodes of bacterial exacerbation of eczema; 15% of these were severe enough to require hospitalization [2]. In the pediatric 1-year study of 0.1% tacrolimus ointment, the incidence of skin infection was 11%, with two patients (<1%) requiring hospitalization for skin infection.

Eczema herpeticum is a well-known complication of atopic dermatitis [3, 4]. Affected patients are no longer primarily young children; the incidence in adults with atopic dermatitis appears to be increasing. A dermatological center in Europe reported on average 1 case per year between 1969 and 1981 but 10 to 15 cases per year between 1982 and 1986, with approximately half of these cases involving adult patients [5]. One child (<1%) and six adults (2%) in the two long-term core studies were diagnosed with eczema herpeticum.

Another common viral skin infection, molluscum contagiosum, has been reported to occur in about 4% of children with atopic dermatitis [6]; there were six cases (2%) of molluscum contagiosum in the long-term pediatric core study. In a study involving 955 atopic dermatitis patients, 7% with active disease had a history of herpes zoster [7]. In the long-term pediatric core study, herpes zoster was reported for eight (3%) patients; seven patients (six of whom were 2-6 years of age) had *chicken pox* and one 14 year-old patient had *shingles*.

The most common serious adverse event in pediatric Study 96-0-025 was asthma occurring in 10 patients, each of whom had a prior history of asthma. Three serious adverse events were considered potentially related to study drug (skin infection, asthma, and Kaposi's varicelliform eruption [eczema herpeticum]). In adult Study FG-06-12, the

most common serious adverse event was a scheduled routine procedure of no relationship to study drug (5/16 patients with serious adverse events). Five serious adverse events were assessed by the investigator as having a causal relationship to the study drug; these events were eczema herpeticum, herpes zoster (varicella), Staphylococcus superinfection, lack of drug effect, and cellulitis (only the last of three episodes was considered to have a relationship to tacrolimus ointment). These events might be anticipated in a population with underlying atopic diathesis.

9.3.2 Adverse Events Leading To Discontinuation

In the long-term safety studies, 10 (3.9%) pediatric patients and 28 (8.9%) adult patients had an adverse event that resulted in discontinuation. Summaries of the adverse events leading to discontinuation in pediatric Study 96-0-025 and adult Study FG-06-12 are presented in Table 32 and Table 33.

Table 32: Adverse Events Leading to Discontinuation: Pediatric Long-Term Study

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

Patient population: all enrolled patients who received at least one dose of study drug. SGOT = serum glutamic oxaloacetic transaminase. LDH = lactate dehydrogenase. Outcome: R=recovered with no residual effects; P=persistent condition at the last study visit. Adverse event days: /- adverse event ongoing at end of study. † Patient No. 158047 had elevated LDH and SGOT at baseline. # Patient allergic to grass, cats, and dogs; reaction occurred 3-4 hours after morning application; treated with Benadryl®. ## *Pain due to infected atopic dermatitis*.
Source: NDA 50-777, Study Report R98-0213-506-C3-E (Appendices 14.4.4.1 and 14.6).

Table 33: Adverse Events Leading to Discontinuation: Adult Long-Term Study

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

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(Table 33 continued)

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

† Defined as highly probable, probable, possible, not assessable, or if relationship to study drug was missing. § At both treated and non-treated areas.
‡ This patient had enlarged lymph nodes at a non-treated site associated with a skin infection (swelling) at a treated area.
†† This 27-year-old male had elevated SGOT and SGPT at Week 1 and Months 2 and 3. The elevated levels resolved at Month 4 at the time of study drug discontinuation. The patient was withdrawn based on Day 110 values (SGOT 53 U/L, SGPT 120 U/L); Month 4 values were SGOT 24 U/L and SGPT 33 U/L.
Source: NDA 50-777, Study Report FG98-506-07 (Appendix 14.4.6.2).

9.4 Exposure and Adverse Events: Tacrolimus Blood Concentration and Adverse Events in the 12-Week Double-Blind Core Studies

An analysis was performed using adverse event data from patients in the three 12-week, double-blind studies who had blood collected for the determination of tacrolimus blood concentration. Adverse events which showed a statistically significant difference in incidence between either tacrolimus ointment group and vehicle group were examined.

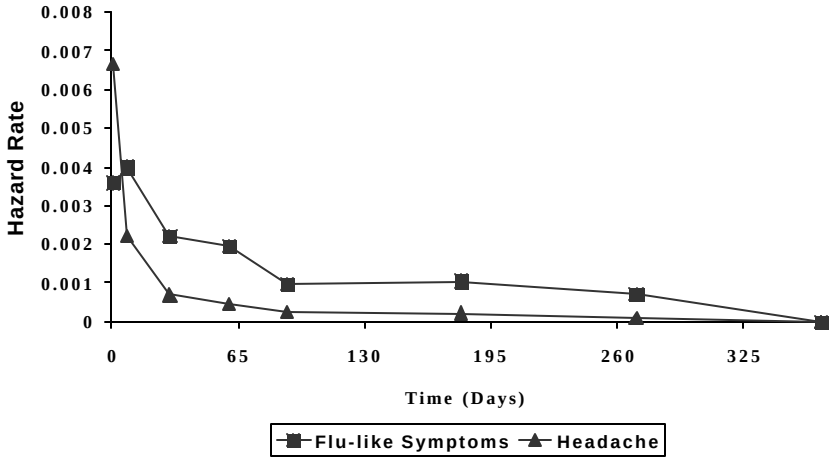
There was no statistically significant difference in the incidence of nonapplication site adverse events between patients with quantifiable tacrolimus blood concentrations (≥ 0.5 ng/mL) and those without quantifiable levels.

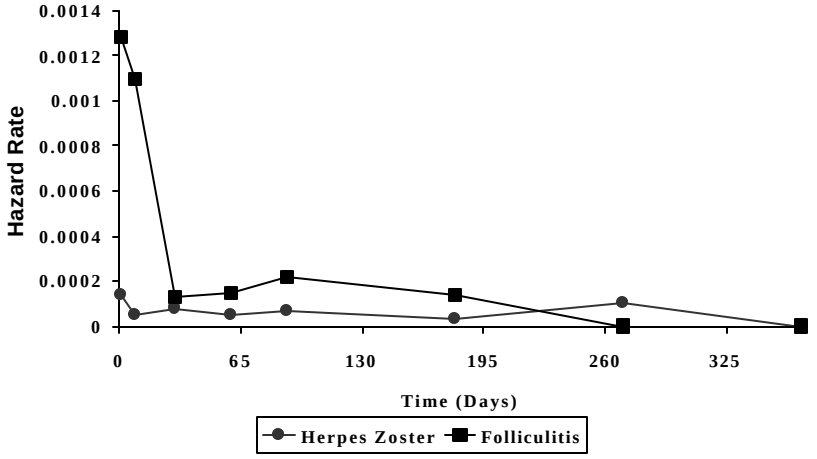
9.5 Exposure and Adverse Events: Hazard Rates for Five Core Studies

In order to explore the potential relationship between drug exposure over time and the incidence of adverse events, time to onset analyses were performed for adverse events considered to be of particular interest in this patient population. These events do not include local irritation events since these have been demonstrated to occur early (generally during the first week) in treatment and might be anticipated given the very sensitive nature of the skin in patients with atopic dermatitis. Analyses were performed using data from the five core studies; the three vehicle-controlled, 12-week double-blind (Studies 97-0-037, 97-0-035, 97-0-036) and the two long-term safety (Study 96-0-025 and FG-06-12) studies. A total of 899 patients were treated with 0.1% tacrolimus ointment in the five core studies and were included in these analyses. Note that all five studies contributed to the analyses from Day 1 through Day 89 but that only long-term study patients were included from Day 90 onward.

Hazard rates for adverse events either remained the same or decreased over time for all treatment groups. Therefore, there is no indication of increased risk for adverse events over time, even with long-term use of 0.1% tacrolimus ointment. Time to event analysis results for the two most common nonapplication site adverse events (flu-like symptoms and headache) and two infections of interest in this patient population (varicella [COSTART zoster] and folliculitis) are shown in Figure 23.

Figure 23: Five Core Studies: Hazard Rates For Adverse Events Of Special Interest





9.6 Laboratory Profiles: Five Core Studies

No trends in laboratory profile suggestive of a safety concern were observed in either the 12-week, double-blind or the long-term studies. As can be expected in patients with atopic dermatitis, eosinophil count, IgE, and LDH were elevated in many patients at baseline and remained so during the studies. Mean and median values for all other parameters remained within normal ranges throughout the study. Baseline mean value and mean change from baseline for laboratory parameters of special interest in the 12-week, double-blind studies (combined data) and the two long-term studies are shown in Table 34 and Table 35.

Very few patients (<1%, 4/1554) discontinued due to a laboratory parameter-related adverse event (see also 9.1.1, Section 9.1.3 and Section 9.3.2). Two patients in the adult 12-week double-blind Study 96-0-035, one white female in the vehicle group and one African American female in the 0.1% tacrolimus ointment group, discontinued due to leukopenia.

The tacrolimus-treated patient was later diagnosed by an independent consultant as having benign neutropenia of African Americans (Section 9.1.1). After reviewing the patient's past medical history and current medications, the independent consultant concluded that the variations observed in her absolute neutrophil count were not inconsistent with the known patterns of this syndrome.

A 3-year old African American male entered the pediatric long-term safety Study 96-0-025 with elevated SGOT and LDH (48 U/L and 381 U/L, respectively). On study day 15, values for both parameters remained outside the normal range (SGOT 51 U/L, LDH 393 U/L); the patient discontinued on day 29.

A 27-year-old male in adult long-term safety study FG-06-12 showed elevated SGOT (98 U/L; within normal range) and SGPT (128 U/L, 120 U/L) at the Month 3 (time of study drug discontinuation) and Month 4 visits. Approximately 1 month later, at the end of study visit, these values were within normal range.

Table 34: Laboratory Profile in Three 12-Week Double-Blind Studies Combined

Parameter		Vehicle	Tacrolimus Ointment	
			0.03%	0.1%
Hemoglobin (g/dL)	Baseline	13.98 n = 237	13.98 n = 233	13.89 n = 234
	Change To EOT	-0.19 ± 0.70 n = 236	-0.20 ± 0.69 n = 233	-0.20 ± 0.71 n = 232
Hematocrit (%)	Baseline	41.6 n = 237	41.6 n = 233	41.4 n = 234
	Change To EOT	-0.6 ± 2.3 n = 236	-0.5 ± 2.4 n = 233	-0.5 ± 2.3 n = 232
WBC Count (10^9/L)	Baseline	7.19 n =237	7.13 n = 226	7.37 n = 229
	Change To EOT	0.22 ± 1.38 n = 236	0.06 ± 2.18 n = 226	-0.35 ± 1.42 n = 227
Serum Creatinine (mg/dL)	Baseline	0.85 n = 235	0.86 n = 233	0.84 n = 237
	Change To EOT	-0.00 ± 0.11 n = 235	-0.00 ± 0.11 n = 233	-0.01 ± 0.1 n = 235
BUN (mg/dL)	Baseline	11.8 n = 235	11.9 n = 233	11.9 n = 237
	Change To EOT	-0.1 ± 3.1 n = 235	0.2 ± 3.3 n = 233	-0.2 ± 3.1 n = 235
SGOT (U/L)	Baseline	29.1 n = 235	28.8 n = 233	29.2 n = 237
	Change To EOT	-0.1 ± 7.9 n = 235	-1.3 ± 8.9 n = 233	-1.2 ± 11.1 n = 235
SGPT (U/L)	Baseline	30.0 n = 235	28.4 n = 233	29.0 n = 237
	Change To EOT	-1.3 ± 14.1 n = 235	-1.2 ± 9.5 n = 233	-1.9 ± 8.2 n = 235
Magnesium (mg/dL)	Baseline	1.83 n = 235	1.83 n = 233	1.82 n = 237
	Change To EOT	-0.01 ± 0.14 n = 235	0.0 ± 0.14 n = 233	0.0 ± 0.15 n = 235

Table continued on next page

Table 34 continued

Parameter		Vehicle	Tacrolimus Ointment	
			0.03%	0.1%
Potassium (mmol/L)	Baseline	4.24 n = 235	4.25 n = 231	4.21 n = 236
	Change to EOT	-0.05 ± 0.46 n = 235	-0.06 ± 0.49 n = 231	-0.03 ± 0.38 n = 234
Glucose (mg/dL)	Baseline	90.2 n = 236	90.7 n = 233	88.8 n = 236
	Change to EOT	-0.5 ± 25.9 n = 236	3.0± 19.9 n – 233	0.3 ± 17.9 n = 234

EOT: end of treatment

Table 35: Laboratory Profile in Two Long-Term Safety Studies

Parameter		0.1% Tacrolimus Ointment	
		Pediatric 96-0-025	**Adult FG-06-12**
Hemoglobin (g/dL)	Baseline	12.83 ± 1.01 n = 251	14.09 ± 1.19 n = 302
	Change To EOS	-0.08 ± 0.79 n = 228	-0.07 ± 0.68 n = 301
Hematocrit (%)	Baseline	38.0 ± 2.9 n = 251	39.1 ± 3.1 n = 299
	Change To EOS	0.3 ± 2.5 n = 228	0.7 ± 2.6 n = 298
WBC Count (10^9/L)	Baseline	7.92 ± 2.29 n = 248	7.04 ± 1.82 n = 302
	Change To EOS	-0.34 ± 2.26 n = 223	-0.045 ± 1.80 n = 301
Serum Creatine (mg/dL)	Baseline	0.56 ± 0.13 n = 254	0.78 ± .13 n = 308
	Change To EOS	0.0 ± 0.08 n = 229	-0.02 ± 0.09 n = 307
BUN (mg/dL)	Baseline	11.6 ± 3.2 n = 254	12.86 ± 3.53 n = 308
	Change To EOS	-0.9 ± 3.2 n = 229	-0.32 ± 3.25 n = 307
SGOT (U/L)	Baseline	33.4 ± 8.7 n = 254	23.4 ± 7.9 n = 300
	Change To EOS	-1.8 ± 6.7 n = 229	-1.3 ± 6.9 n= 299
SGPT (U/L)	Baseline	23.3 ± 8.2 n = 253	22.0 ± 14.7 n = 300
	Change To EOS	-1.7 ± 7.2 n = 228	-2.2 ± 11.3 n = 299
Magnesium (mg/dL)	Baseline	1.86 ± 0.35 n = 254	2.15 ± 0.23 n = 308
	Change To EOS	-0.01 ± 0.39 n = 229	0.05 ± 0.29 n = 307

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Table 35 continued

Parameter		0.1% Tacrolimus Ointment	
		Pediatric 96-0-025	**Adult FG-06-12**
Potassium (mmol/L)	Baseline	4.21 ± 0.33 n = 253	4.32 ± 0.33 n = 306
	Change To EOS	-0.01 ± 0.46 n = 228	-0.02 ± 0.39 n = 305
Glucose (mg/dL)	Baseline	85.5 ± 14.4 n = 254	92.49 ± 18.41 n = 299
	Change To EOS	-0.7 ± 19.1 n = 229	2.49 ± 18.70 n = 298

EOS: end of study

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10 QUALITY OF LIFE

Atopic dermatitis can significantly impact a patient's life, hindering social interaction, lowering self-esteem, leading to work/school absenteeism, negatively affecting family interactions, and producing sleep disturbances and emotional distress [1, 2, 3]. A quality of life questionnaire was completed by patients/parents/guardians in the three pivotal studies (Studies 97-0-037, 97-0-035, 97-0-036); three questionnaires were used: The Children's Dermatology Life Quality Index (CDLQI, children 5 to 15 years of age), a modified CDLQI (toddlers 2 to 4 years of age) and the Dermatology Life Quality Index (DLQI; adults ≥16 years of age) [4, 5]. Compared with those applying vehicle, patients treated with 0.03% or 0.1% tacrolimus ointment had significant quality of life benefits in the areas of symptoms and feelings, everyday activities, personal relationships, sleep, and treatment impact.

In children, the most substantial improvements were in the areas of sleep, and symptoms and feelings. In adults, statistically significantly greater improvements in the quality of life were observed in patients treated with the 0.1% tacrolimus ointment concentration compared with those treated with the 0.03% tacrolimus ointment concentration (Table 36).

Table 36: Change from Baseline to End of Treatment in Total Quality of Life Score

Age Group		Treatment Group		
		Vehicle	Concentration of Tacrolimus Ointment	
			0.03%	0.1%
Toddlers	*n = 145*	n=48	n=51	n=46
	LSMean ± SE	-7.9 ± 2.8	-30.8 ± 2.7	-35.6 ± 2.8
Children	*n = 178*	n=55	n=58	n=65
	LSMean ± SE	-8.1 ± 2.2	-24.4 ± 2.1	-24.1 ± 2.0
Adults	*n = 579*	n=191	n=195	n=193
	LSMean ± SE	-5.6 ± 1.4	-21.1 ± 1.4	-27.1 ± 1.4
		p-Value (analysis of covariance)		
		0.03% vs Vehicle	0.1% vs Vehicle	0.03% vs 0.1%
Toddlers		<0.001	<0.001	0.224
Children		<0.001	<0.001	0.937
Adults		<0.001	<0.001	0.003

Patient population: all randomized patients who were dispensed study drug (applied study drug at least once) and who had both a baseline and at least one other quality-of-life assessment.
Score is adjusted for baseline. LS=least squares mean SE=standard error

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11 SUMMARY OF 0.1% TACROLIMUS OINTMENT VERSUS 0.03% TACROLIMUS OINTMENT

Both tacrolimus ointment concentrations were effective in the treatment of atopic dermatitis. The 0.1% tacrolimus ointment concentration had greater therapeutic benefit than the 0.03% concentration. Based on combined analyses of the three 12-week, double-blind studies:

- Statistically significantly more patients achieved ≥90% clinical improvement with 0.1% tacrolimus ointment compared with 0.03% tacrolimus ointment (38% versus 31%, p=0.038).

- The greater therapeutic benefit of 0.1% tacrolimus ointment was particularly evident in adult patients, all patients with severe atopic dermatitis at baseline, and all patients with extensive (≥75% BSA affected) disease involvement. The data also suggest a greater therapeutic benefit with the 0.1% tacrolimus ointment concentration compared with the 0.03% concentration for African American adults. For African American adult patients, those administered the 0.1% tacrolimus ointment concentration had a numerically higher success rate than those applying 0.03% tacrolimus ointment (29% versus 16%).

- The 0.1% tacrolimus ointment concentration was more effective than the 0.03% concentration based on the distribution of responses in the Physician's Global Evaluation. Clinically relevant moderate improvement or better (≥ 50% improvement) was observed in 66% of patients in the 0.03% tacrolimus ointment group and 75% in the 0.1% tacrolimus ointment group.

- The 0.1% tacrolimus ointment concentration was statistically more effective than the 0.03% concentration for improvement in EASI score; representative scores for edema, excoriation, and scaling; and percent BSA affected. A trend toward greater improvement with the 0.1% tacrolimus ointment concentration was observed with respect to Total Score for the individual signs of atopic dermatitis.

- In adults, statistically significantly greater improvements in the quality of life were observed in patients treated with the 0.1% tacrolimus ointment concentration compared with those treated with the 0.03% tacrolimus ointment concentration.

The therapeutic benefit of 0.1% tacrolimus ointment was achieved without a substantial increase in risk. In the 12-week, double-blind studies, no adverse event had a statistically significantly higher 12-week adjusted rate in the 0.1% tacrolimus ointment group compared with the 0.03% tacrolimus ointment group. In the two long-term safety studies evaluating 0.1% tacrolimus ointment, the incidence of nonapplication site adverse events, including those related to the gastrointestinal system, the nervous system (e.g., headache), and infections did not increase with increasing duration of study drug exposure or cumulative amount of ointment used.

Both concentrations of tacrolimus ointment are effective additions to the physician's armamentarium for the treatment of atopic dermatitis. The availability of both concentrations provides physicians with a needed therapeutic flexibility so that they may tailor treatment to patient needs.

12 OVERALL SUMMARY OF RISK/BENEFIT

Tacrolimus ointment (0.03% and 0.1%) represents a safe and effective nonsteroidal topical therapy for the management of atopic dermatitis in both adult and pediatric patients. Tacrolimus ointment (0.03%, 0.1%):

- is effective in the treatment of atopic dermatitis, even in severe cases with extensive disease involvement.

  Clinical response (at least moderate improvement) is generally observed within 1 week. In addition, the patient rapidly perceives a noticeable cosmetic response and symptom relief (especially pruritus relief).

- can be safely used on the face and neck and intertriginous areas.

  There is no evidence of an increased risk for adverse events when tacrolimus ointment is applied to the face and neck compared with other parts of the body, including skin atrophy or other skin disorders observed with topical steroids.

- can be safely used in pediatric patients even in young children (2 to 6 years of age).

  There is no evidence of increased risk for pediatric patients compared with adults nor for young children compared with older children. It is safe, even in young children with severe and/or extensive body surface area involvement.

- is safe and effective with chronic daily use.

  When used daily for up to 1 year, there is

  - no suggestion of a loss of effectiveness.
  - no skin atrophy, striae, hypopigmentation or other skin disorders.
  - no increase in adverse events.

The risks associated with the use of tacrolimus ointment are minimal. Adverse events are either benign (skin tingling, alcohol intolerance), local irritation events of short duration occurring early in treatment (pruritus, skin burning), low incidence events (acne, folliculitis, hyperesthesia, dyspepsia, herpes zoster, cyst, myalgia), or occur at an incidence consistent with that observed in the general population (flu-like symptoms, headache).

No adverse event had a statistically higher incidence in the 0.1% tacrolimus ointment group compared with the 0.03% tacrolimus ointment group in the double-blind studies. The 0.1% tacrolimus ointment concentration had a greater therapeutic benefit than the 0.03% concentration, especially for patients with severe or extensive disease, adult patients and African American adults.

In summary, patients with moderate to severe atopic dermatitis have limited therapeutic options; those currently available (e.g., mid- to high-potency topical steroids, systemic steroids, PUVA , etc.) carry such potential risks as skin atrophy, hypopigmentation, striae, telangiectases, secondary infections, acne, skin hemorrhage after minor trauma, hypothalamic-pituitary-adrenal (HPA) axis suppression, growth retardation, and cutaneous malignant lesions.

Patients treated with current therapies often have to take “drug holidays” to minimize the risk of side effects. These holidays can lead to frequent flares and complications like skin infections.

In current practice, patients with resistant disease undergoing topical steroidal therapy often require periodic systemic steroidal pulses or other concomitant medication which increases their risk for adverse events.

Tacrolimus ointment represents a novel, safe and effective, nonsteroidal topical therapy for the management of atopic dermatitis in both adult and pediatric patients.