Drug Class Review

Topical Calcineurin Inhibitors

Final Report
Evidence Tables

October 2008

The Agency for Healthcare Research and
Quality has not yet seen or approved this report.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Nancy J. Lee, PharmD, BCPS
Marian McDonagh, PharmD
Benjamin Chan, MS
Kimberly Peterson, MS
Sujata Thakurta, MPA:HA

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Prepared for: Drug Effectiveness Review Project
Principal Investigator, Marian McDonagh, Pharm D

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Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Aims	Databases searched; Literature search dates; Other data sources	Eligibility criteria	Number of trials/ Number of patients	Characteristics of identified articles: study designs
Ashcroft 2005	To determine the efficacy and tolerability of topical pimecrolimus and tacrolimus compared with other treatments for atopic dermatitis	MEDLINE, EMBASE, Cochrane library (including Cochrane Skin Group specialized register, and the Cochrane central register of controlled trials) to December 2004; searched reference lists of all retrieved trials along with the websites for the European Agency for the Evaluation of Medicinal Products and the US Food and Drug Administration; used search terms “pimecrolimus”, “Elidel”, “SDZ ASM 981”,“tacrolimus”, “Protopic”, and “FK506”	Randomized controlled trials that compared topical pimecrolimus or topical tacrolimus at a licensed therapeutic dose with vehicle or another active treatment in patients with atopic dermatitis, and that reported efficacy outcomes or adverse events (tolerability); excluded trials with non-relevant outcomes and healthy volunteers	25 randomised controlled trials (totaling 6897 patients)	Pimecrolimus – 11 trials total; 8 vehicle-controlled, 3 with active comparators, 1 head-to-head study Tacrolimus – 14 trials total; 7 vehicle-controlled, 7 with active comparators

Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions
Ashcroft 2005	Infants, children, and adults with atopic dermatitis of varying severity	5 of 25 studies had study durations ≥ 24 weeks; remaining were 3-12 weeks in duration 11 pimecrolimus trials included: 437 infants, 1222 children, and 1029 adults with varying degrees of disease severity 14 tacrolimus trials included: 1497 children and 2712 adults with moderate to severe disease 7 trials: Pimecrolimus 1% twice daily vs. vehicle 1 trial: Pimecrolimus 1% four times daily vs. Pimecrolimus 1% twice daily 1 trial: Pimecrolimus 0.05%, 0.2%, 0.6%, and 1% twice daily vs. vehicle or betamethasone-17-valerate 0.1% 1 trial: Pimecrolimus 1% twice daily vs. triamcinolone acetonide 0.1% + hydrocortisone acetate 1% 1 trial: Pimecrolimus 1% twice daily vs. Tacrolimus 0.03% twice daily 4 trials: Tacrolimus 0.03% and 0.1% twice daily vs. vehicle 3 trials: Tacrolimus 0.03%, 0.1%, and 0.3% twice daily vs. vehicle 1 trial: Tacrolimus 0.1% twice daily vs. betamethasone valerate 0.1% 1 trial: Tacrolimus 0.1% twice daily vs. aclometasone dipropionate 0.1% 1 trial: Tacrolimus 0.1% twice daily vs. oral cyclosporin 3 mg/kg once daily 1 trial: Tacrolimus 0.03% and 0.1% twice daily vs. hydrocortisone butyrate 0.1% 1 trial: Tacrolimus 0.03% and 0.1% twice daily vs. hydrocortisone acetate 1%

Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Main efficacy outcome
Ashcroft 2005	Primary outcomes: the investigators' rating of the global degree of improvement (for pimecrolimus, used the proportion of patients who were rated by the investigator as clear or almost clear; for tacrolimus trials, used the proportion of patients who achieved at least 90% improvement from baseline, defined as clear or excellent improvement in the trials) Secondary outcomes: patient global assessment of feeling much better or better, percent of patients with flares, and improvements in QoL

Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Main efficacy results
Ashcroft 2005	For primary outcome: The pooled rate ratio of 5 pimecrolimus vehicle-controlled trials showed that pimecrolimus was significantly more effective than vehicle (pooled RR 2.72, 95% CI, 1.84 to 4.03). One longer term study (Kapp, 2002) found no significant difference between pimecrolimus and vehicle for the proportion of patients with clear or almost clear disease. One tacrolimus trial found that tacrolimus 0.03% ointment was significantly more effective than vehicle (RR 2.13, 95% CI, 1.24 to 3.68), however the response observed between tacrolimus 0.1% ointment and vehicle were not significantly different (RR1.57, 95% CI, 0.88 to 2.81) . Three other vehicle-controlled trials found that tacrolimus 0.03% and 0.1% ointment were significantly more effective than vehicle at 12 weeks. Pooled rate ratios for patient assessment of disease control favored tacrolimus over vehicle. Betamethasone valerate (potent topical steroid) was significantly more effective than pimecrolimus at 3 weeks. Treatment with triamcinolone acetonide 0.1% (trunk/limbs) + hydrocortisone acetate 1% (face/neck) was as effective as treatment with pimecrolimus at 52 weeks. Approximately, 41% of pime When compared with mild topical steroids, tacrolimus 0.03% and 0.1% ointment were more effective th When compared with hydrocortisone butyrate 0.1%, tacrolimus 0.03% was less effective while tacrolim Tacrolimus 0.1% was more effective than a combination of hydrocortisone butyrate 0.1% (trunk/limbs) Tacrolimus 0.03% was not significantly different from pimecrolimus at 6 weeks.

Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Harms results
Ashcroft 2005	The most common adverse effects reported related to skin irritation and skin burning: Pimecrolimus 1% and vehicle did not differ significantly in the incidence of skin burning (pooled rate ratio obtained from six trials was 0.87, 95% CI, 0.70 to 1.09), but the rate of skin burning was significantly higher with pimecrolimus 1% than with betamethasone valerate 0.1% (RR 5.26, 95% CI, 1.92 to 14.30) or a combined regimen of triamcinolone acetonide 0.1% and hydrocortisone acetate 1% (RR 2.38, 95% CI, 1.66 to 3.40). Tacrolimus 0.03% and tacrolimus 0.1% were significantly more likely to cause skin burning than vehicle (pooled rate ratios 1.89, 95% CI, 1.43 to 2.50; and RR 2.08, 95% CI, 1.35 to 3.18). Both tacrolimus 0.03% and tacrolimus 0.1% were significantly more likely to cause skin burning than were mild or potent topical corticosteroids. The incidence of skin infections was not significantly different in any of the comparisons of pimecrolimus or tacrolimus with control (active or vehicle). None of the trials reported on key adverse effects such as thinning of skin or adrenal gland suppression.

Evidence Table 1. Systematic review of topical calcineurin inhibitors

Author Year	Quality assessment method	Limitations of primary studies	Data synthesis methods	Comments
Ashcroft 2005	Trial eligibility was determined by two authors; trials were rated for methodological quality using the Jadad scale and scored out of a maximum of five	Analyses of rates of withdrawals and adverse events were based on data pooled from trials of different durations; heterogeneity in the patient population (infants, children, adults), the severity of the disease, and the choice of topical corticosteroid; use of investigators' global assessments of response to treatment also causes some concern (despite such assessments of response to treatment being widely used as outcome measures in clinical trials of atopic dermatitis, further research is needed to fully determine their validity, reliability, and sensitivity to change)	Not all of the trials reported on all the outcomes of interest. For each comparison and outcome investigators undertook separate meta-analyses, grouping the topical corticosteroids on the basis of their potencies: mild (aclometasone dipropionate 0.1%, hydrocortisone acetate 1%) and potent (betamethasone valerate 0.1%, hydrocortisone butyrate 0.1%, triamcinolone acetonide 0.1%).They also stratified the analysis of efficacy data by the duration of treatment. Summarized dichotomous data as rate ratios (relative risks) and combined these by using a random effects model; results given with 95% confidence intervals; computed homogeneity statistics to test the agreement of the individual trial results with the combined meta-analytical summary; analyses were carried out in RevMan version 4.2.6.	

Evidence Table 2. Quality assessment of systematic reviews of topical calcineurin inhibitors

Study	Searches through	1. Search methods reported?	2. Comprehensive search?	3. Inclusion criteria reported?	4. Selection bias avoided?	5. Validity criteria reported?
Ashcroft, 2005	December 2004	Yes Medline,EMBASE, Cochrane Skin Groupregister, Cochrane central register of controlled trials, websites for Europena Agency for the Evaluation of Medicinal Products, US Food and Drug Administration, hand-searching reference lists; search terms were reported	Yes	Yes Included randomized controlled trials that compared topical calcineurin inhibitors at a licensed dose with vehicle or an active comparator; did not exclude trials based on language or publication status	Yes Dual review of abstracted data and quality assessment	Yes Reported quality ratings

Evidence Table 2. Quality assessment of systematic reviews of topical calcineurin inhibitors

Study	6. Validity assessed appropriately?	7. Methods used to combine studies reported?	8. Findings combined appropriately?	9. Conclusions supported by data?	10. Overall scientific quality (score 1-7)
Ashcroft, 2005	Yes, authors provided quality rating scores but did not comment on 4 trials which had ratings of 1-2 of 5	Yes	Yes Tests for heterogeneity were reported when applicable	Yes	6 of 7

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Study Design/ Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?	Interventions
Kempers, 2004 US Fair	Investigator-blinded, multicenter (17 derm clinics, 2 allergy/immunology centers)	2-17 years with moderate atopic dermatitis (with an IGA score of 3) Those treated with phottherapy within 1 mo prior to 1st use of study med were excluded as were patients who received topical therapywithin 7 days, systemic corticosteroids within 1 mo, or systemic antibiotics within 2 weeks prior to 1st use of study medication	NR	Pimecrolimus 1% cream versus tacrolimus 0.03% ointment; applied twice daily x 6 weeks

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity
Kempers, 2004 US Fair	NR/NR	Nonmedicated emollients for non-leisonal areas	Investigator Global Assessment scores on day 4, 8, 15, 22, 29, 36, and 43 Measuring local tolerability using 2 questionnaires (complete version used on day 43 and abridged version used on day 4, 8, 15, 22, 29, and 36) on application site reactions Patient evaluation of pruritus severity score for the 24 -hr period before clinic visit Absence or presence of oozing/crusting, hyperpigmentation, hypopigmentation, dry skin/xerosis	Mean age not reported. 82-86% were 2-12 yrs 14-18% were 13-17 yrs Female 56% White 44-63% Black 18-20 Asian 4-6% Other 14-30%

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kempers, 2004 US Fair	IGA score 3 (moderate) 99% 4 (severe) 1% Pruritus score 1 (mild) 19-20% 2 (moderate) 35-47% 3 (severe) 33-42% Mean duration of AD 79-79.5 mos (SD 40.2-51.6) Mean age of onset: 1.6-1.8 yrs (SD 2.4-2.9) Presence of AD (%) Head/neck: 74-80% Trunk 78-80% Upper limbs 97-99% Lower limbs 94-99%	170 NR 141	11.3% (16/141) 2 Efficacy: 139 Safety: 141

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QoL, treatment failure (use of other agents)	Method of adverse effects assessment	Adverse events
Kempers, 2004 US Fair	% of patients with IGA score of 0 or 1 (clear or almost clear) at day 43: Pimecrolimus: 30% Tacrolimus: 42% p-value: NSD % of patients with pruritus score of 0 or 1 (absent or mild) at day 43: Pimecrolimus: 64% Tacrolimus: 70% p-value: NSD Change from baseline in BSA affected by body region at day 43 (ITT) for pimecrolimus vs. tacrolimus: Whole body: 43.3% vs. 44.5%, p-value= NSD Head/neck: 53.7% vs. 34.9%, p-value= NSD Lower limbs: 29.3% vs. 41.9%, p-value= NSD Upper limbs: 35.3% vs. 38.0%, p-value= NSD	AE monitoring and recording were done by unknown personnel. Labs and VS measured at baseline and day 43. Local tolerability of application site reactions was measured/assessed with 2 questionnaires by study investigator.	Composite application site reactions (at day 4) were experienced by 24% of pimecrolimus-treated patients compared with 26% of tacrolimus-treated patients. For individual components of application site reactions (at day 4)--results based on "observed" group: More tacrolimus-treated patients reported itching (20% vs. 8%), warmth/stinging (17$ vs. 20%) compared with pimecrolimus (p-value= NSD) More tacromims-treated patients reported erythema/irritation (19% vs. 8%) compared with pimecrolimus (p-value= 0.39) % of patients with AE other than application site reactions for pimecrolimus vs. tacrolimus: Herpes simplex: 3% vs. 1% Staph infection NOS: 4% vs. 0% Impetigo NOS: 0% vs. 3% Atopic Derm NOS: 1% vs. 3% Pruritus NOS: 0% vs. 3% Rash NOS: 0% vs. 3% Erthyema: 0% vs. 3%

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Kempers, 2004 US Fair	16 (11.3%) 2 (1.4%)	Primary endpoint: local tolerability outcome (ie, application site reactions) Secondary endpoint: efficacy and safety Although measures were taken to ensure that investigators were blinded, it is unclear if these were adequate in maintaining the blinding throughout the study duration There is a higher differential for total withdrawal for pimecrolimus compared with tacrolimus (18.6% vs. 4.3%)

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Study Design/ Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?	Interventions
Paller, 2005 US, Canada Fair	Combined analysis of 3 prospective, randomized, multicenter, investigator-blinded trials (all with the same study design)	2 trials enrolled those 2-17yrs; 1 trial enrolled those >16 yrs (considered to be adults by the author) All patients had to meet the clinical criteria of Hanifin and Rajka15 for the diagnosis of AD and have disease over at least 5% of their total body surface area (BSA). The severity of disease was rated according to the IGADA. Key exclusion criteria were any skin disorder other than AD in the area(s) to be treated in the study, extensive scarring or pigmentation in the area(s) to be treated in the study, or clinically infected AD. Patients whose disease would require the use of nonsteroidal immunosuppressants, light therapy, systemic and topical corticosteroids, topical H1 and H2 antihistamines, topical antimicrobials, and any other medicated topical agent were excluded from the study.	NR	Tacrolimus ointment or pimecrolimus cream; applied twice daily x 6 weeks or until 1 week after the affected areas was completely cleared (whichever came first).

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity
Paller, 2005 US, Canada Fair	Run-in: NR Washout: at least 4 weeks depending on prior treatment	Nonmedicated topical agents (such as emollients) were permitted only in the areas not being treated with study medication. Intranasal or inhaled corticosteroids were permitted if use was restricted to indications approved by the Food and Drug Administration and doses did not exceed the maximal approved doses. Use of sunscreens was permitted throughout the study.	EASI, treatment success based on Investigator Global AD Assessment, % reduction in affected BSA, reduction in itch Baseline, weeks 1, 3, 6	Data for each trial are presented below in the order of tacrolimus and pimecrolimus. Pooled results were not abstracted.

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Paller, 2005 US, Canada Fair	Pooled results were not abstracted	Pooled results were not abstracted	Pooled results were not abstracted

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QoL, treatment failure (use of other agents)	Method of adverse effects assessment	Adverse events
Paller, 2005 US, Canada Fair	Pooled results were not abstracted	NR	Pooled results were not abstracted

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Paller, 2005 US, Canada Fair	Pooled results were not abstracted	

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Study Design/ Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?	Interventions
(a) Children with mild disease	see above	see above	see above	Tacrolimus 0.03% ointment vs. pimecrolimus 1% cream
(b) Children with moderate to severe disease	see above	see above	see above	Tacrolimus 0.1% ointment vs. pimecrolimus 1% cream

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity
(a) Children with mild disease	see above	see above	see above	6.3-6.5 yrs (SD3.7-3.8) Female 52.9-57.1% White 42.4-46.2% Black 26.4-28.6% Other 27.4-29.0%
(b) Children with moderate to severe disease	see above	see above	see above	6.3-6.5 yrs (SD 3.9) Female 44.2-49.1% White 38.4-39.8% Black 39.8-41.1% Other 20.4-20.5%

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
(a) Children with mild disease	IGADA scores: Mild: 100% vs. 100% Mean EASI score: 5.2-5.4 Mean BSA: 13.8% Head/neck involvement: 65.7-66.7%	NR NR 425	103 (24.2%) 57 423
(b) Children with moderate to severe disease	IGADA scores: Mild: 0.9-1.8% Moderate: 75.2-81.1% Severe: 16.2-21.2% Very Severe: 1.8% Mean EASI score: 16.9-17.4 Mean BSA: 30.8-31.6% Head/neck involvement: 71.2-77.0%	NR NR 226	79 (35%) 32 224

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QoL, treatment failure (use of other agents)	Method of adverse effects assessment	Adverse events
(a) Children with mild disease	% improvement from baseline in EASI score: 52.1% vs. 42.7%, p=0.07 % achieving treatment success (IGADA score of 0 or 1): 46.9% vs. 40.7%, p=NR Reduction in % BSA: 57.1% vs. 50.2%, p=NR Change in pruritus score from baseline: Tacro -2.9 cm (p≤0.01) vs. Pime -2.4 cm	see above	Application site reactions: Burning: 5.3% vs. 9.2% Pruritus: 5.3% vs. 6.5% Pain: 1.9% vs. 1.8% Erythema: 1.0% vs. 1.8% Skin infection: 0.0% vs. 0.0% Acne: 0.5% vs. 0.0% Herpes simplex: 0.5% vs. 0.0% *No eczema herpeticum
(b) Children with moderate to severe disease	% improvement from baseline in EASI score: 67.2% vs. 56.4%, p=0.04 % achieving treatment success (IGADA score of 0 or 1): 32.4% vs. 17.7%, p<0.01 Reduction in % BSA: 64.6% vs. 47.5%, p<0.001 Change in pruritus score from baseline: Tacro -3.7 cm (p≤0.01) vs. Pime -3.0 cm	see above	Application site reactions: Burning: 5.4% vs. 7.1% Pruritus: 5.4% vs. 9.7% Pain: 0.9% vs. 1.8% Erythema: 1.8% vs. 0.9% Skin infection: 1.8% vs. 1.8% Acne: 0.0% vs. 0.0% Herpes simplex: 0.0% vs. 0.0% *No eczema herpeticum

Evidence Table 3. Head-to-head trials of topical calcineurin inhibitors

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
(a) Children with mild disease	103 10	Planned sample size: 400
(b) Children with moderate to severe disease	79 9	Planned sample size: 200

Evidence Table 4. Quality assessment of head-to-head trials of topical calcineurin inhibitors

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kempers, 2004 US	Yes, via randomization numbers (by phone system)	Yes, through automated phone system	There were differences in pruritus scores (moderate and severe) between treatment arms. 42% in pimecrolimus arm reported severe pruritus vs. 33% in tacrolimus arm.	Yes	Yes	No	No
Paller, 2005	Yes, via sequential randomization numbers (by phone system)	Yes, through automated phone system	Yes	Yes	Yes	No	No

Evidence Table 4. Quality assessment of head-to-head trials of topical calcineurin inhibitors

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Withdrawal: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Kempers, 2004 US	Yes NR NR NR	Yes (Pimecrolimus 18.6% vs. Tacrolimus 4.3%)	Efficacy- ITT with LOCF (98.6% analyzed) Safety- ITT (100% reported) without imputation	No	Fair	Novartis
Paller, 2005	Yes NR NR NR	No/No	Efficacy-evaluable population but end result similar to ITT population (with LOCF)	NR	Fair	Fujisawa

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Belsito, 2004 US Fair	Double-blind, multicenter	> 18 yrs who had 6 wks or longer history of chronic hand AD; IGA score of mild to moderate disease with at least mild scaling and mild erythema of the more severely affected hand was required for enrollment. Those with the following diseases limited to the hands were eligible: dyshidrosis, atopic dermatitis, irritant and allergic contact dermatitis. Exclusion- pregnancy; concurrent disease or treatment that could interfere with study evaluations; hypersensitivity to study drug ingredients; severe vasicullobulous dermattits of the hands; contact utricaria; latex alergey; bullous disorders; hand-foot and mouth disease; mosaic warts; history of malignant disease or current pre-malignant skin conditions of the hands; concurrent flaring of atopic dermatitis; psoriasis or other concurrent skin disease of the hands requiring therapy; patients who used systemic steroids within the previous month, or who used sytemic antibiotics for imfections of the hands or topical therapy for the hands within 7 days before screening.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Belsito, 2004 US Fair	Pimecrolimus 1% cream versus vehicle; applied twice daily x 3 weeks. The evening application was followed by occulsion for at least 6 hours using vinyl gloves. Handwashing (until 3 hours after study drug application) and irritants were to be avoided.	NR	Nonmedicated emollients and/or creams were allowed 1 hour before or after study drug application.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Belsito, 2004 US Fair	Primary endpoint: IGA score (treatment success) Baseline, day 4, 8, 14 and 22.	44.6 yrs Female 59.9% White: 83.7% Nonwhite: 16.3%	IGA score for pimecrolimus and vehicle Almost clear: 0.7% vs 0% Mild disease: 32.5% vs. 25.9% Moderate disease: 64.2% vs. 69.2% Severe disease : 2.6% vs. 4.9% **Suspected** etiology: Irritant contact dermatitis: 41.6% vs. 38.5% Endogenous disease: 30.9% vs. 33.6% Irritant contact dermatitis + endogenouse disease: 13.4% vs. 8.4% Irritant contact dermatitis + allergic contact dermatitis: 10.7% vs. 11.2%	NR NR 294

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Belsito, 2004 US Fair	22 NR 294	% of patients with IGA score of 0 to 1 (treatment success) for pimecrolimus and vehicle: 27.5% vs. 17.5%; (estimated from graph) absolute difference: 10%, p=0.68. Subgroup: % of patients with IGA score of 0 or 1 with palmer involvement Presence of involvement: 23.3% vs. 17.3% Absence of involvement: 42.9% vs. 20.0% Disease patterns: Palmer surface involvement: 76.8% Dorsal involvement : 53.0% Dermatitis on the lateral surface of the fingers: 72.2%

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Belsito, 2004 US Fair	NR	Types of AE were not reported for either treatment arms. "There appeared to be no appreciable differences in the rates of occurrence of common AE in the pimecrolimus-treated and vehicle-treated groups." Application site reactions for pimecrolimus and vehicle: 0.7% vs. 2.1%	22 (7.5%) 6 (types of events not reported for either arms)

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Belsito, 2004 US Fair	

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Breuer, 2004 Germany companion to Kaufmann, 2004	Double-blind, multicenter (19 centers) Randomization 2:1 (pimecrolimus: vehicle)	3–23 mos if they had atopic eczema affecting ≥5% of the body surface area and a baseline IGA score of 2 (mild disease severity) to 5 (very severe disease). Exclusion: insufficient wash-out periods for systemic corticosteroids, antihistamines, antibiotics or other therapies that might have an effect on atopic eczema; concomitant diseases that might interfere with the study; severe concurrent skin disease in the study area, and active viral or bacterial infections.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Breuer, 2004 Germany companion to Kaufmann, 2004	Pimecrolimus 1% cream vs. vehicle; applied twice daily x 4 weeks.	NR/NR	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Breuer, 2004 Germany companion to Kaufmann, 2004	Primary endpoint: EASI score Secondary endpoint: IGA score, SCORAD score, intensity of pruritus/sleep loss and overall assessment of disease assessed by the caregivers	11.5-12.3 mo (SD 5.8-6.1) Female 28.8-37.2% White 90.7-92.4% Black 0-1.6% Asian 5.4-6.1% Other 1.5-2.3%	Height 74.4-75.3 cm (SD 7.2-8.0) Weight 9.4 kg (SD 2.0-2.1) IGA score 2 (mild): 9.3-12.1% 3 (moderate): 58.1-59.1% 4 (severe): 25.8-26.4% 5 (very severe): 3.0-6.2% EASI score: 16.6-17.7 (SD 10.3-10.8) IGA score: 3.2-3.3 (SD 0.7) SCORAD score: 46.9-48.6 (SD 15.0-15.9)	201 NR 196

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Breuer, 2004 Germany companion to Kaufmann, 2004	38 NR 195	Mean EASI score for pimecrolimus and vehicle: Score at 4 weeks: -4.9 (SD 6.0) vs. +17.3 (SD 13.3) % decrease in score from baseline: -71.5% vs. +19.4%, p<0.001 vs. vehicle Mean IGA score: Score at 4 weeks: 1.63 (SD 1.0) vs. 3.0 (SD 1.1) % decrease in score from baseline: -50.7% vs. -5.5%, p<0.001 vs. vehicle Mean SCORAD score from baseline: Score at 4 weeks: 21.8 (SD 16.1) vs. 46.3 (SD 21.7) % decrease in score from baseline: -55.2% vs. -1.1%, p=0.002 vs. vehicle Mean pruritus score: Score at 4 weeks: 2.1 (SD 2.3) vs. +5.2 (SD 3.3), p<0.001 vs. vehicle Mean sleep loss score: Score at 4 weeks: 1.6 (SD 2.3) vs. +4.1 (SD 3.3), p<0.001 vs. vehicle

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Breuer, 2004 Germany companion to Kaufmann, 2004	NR	NR (reported in Kaufmann, 2006)	38 NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Breuer, 2004 Germany	
companion to Kaufmann, 2004	

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	Double-blind, multicenter (25 sites) Randomization 2:1 (pimecrolimus vs. vehicle)	3-23 mos; clear diagnosis of AD, affecting ≥5% of total body surface area and with a baseline IGA of 2 or 3 (mild to moderate) , based on the degree of erythema and infiltration/papulation. Exclusion-immunocompromised; other concurrent or active skin disease or viral skin infections or known sensitivity to study drug; subjects who received phototherapy or systemic treatment known to affect AD within the previous month; topical therapy within the previous week, or sedative antihistamines to treat pruritus within the previous week.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	Pimecrolimus 1% cream versus vehicle; applied twice daily x 6 weeks.	NR/NR	Bland emollients on areas untreated with study medication.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	Primary endpoint: IGA score Secondary endpoint: EASI score; severity of pruruitus made by the caregiver; assessment of the disease by the caregiver Baseline, days 8, 15, 22, 29 and 43.	12.6-12.7 mos (SD 6.25-6.29) Male 54.0-55.3% White 52.8-69.8% Black 6.3-13.0% Asian 1.6-2.4% Other 22.2-31.7%	Height: 74.7-75.0 cm (SD 7.54-8.52) Weight: 9.5-9.8 kg (SD 1.84-1.94) IGA score: 2 (mild): 32.5-33.3% 3 (moderate): 66.7-67.5% mean EASI score: 10.2-11.2 (SD 7.75-7.88)	NR NR 186

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	44/ NR/ 186	IGA score of 0 or 1 at 6 weeks for pimecrolimus and vehicle: 54.5% vs. 23.8%; p<0.001 mean EASI score decreased by: 6.8 points vs. 0.75 points, p<0.001 % decline in overall MEDIAN EASI score: 81.6% vs. 25% % achieving pruritus severity (absent or mild): 72.4% vs. 33.3%; p<0.001 % of caregivers reporting complete or good control of disease: 71.5% vs. 27.0%; p<0.001 Subgroup For those with moderate severity (for pimecrolimus and vehicle): 70% improved/5% worsened vs. 36% improved/14% worsened; p-value=NR For those with mild disease: 65% improved/7.5% worsened vs. 48% improved/43% worsened For those 3 mo to 1 yr with IGA score of 0 to 1 (for pimecrolimus and vehicle): 65.5% vs. 25% For those 1 to 2 yrs with IGA score of 0 to 1: 46.3% vs. 22.6%

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	Investigators sought to identify the cause of AE	74.8% of pimecrolimus-treated patients vs. 65.1% of vehicle-treated patients experienced at least 1-treatment emergent AE. % of AE related to study medication for pimecrolimus and vehicle: 5.7% vs. 12.7% Most common AE were typical childhood infections and ailments (pyrexia, upper respiratory tract infection, nasopharyngitis, teething, and diarrhea); none of these was considered to be study medication related. Pyrexia (31.7% vs. 12.7%) and diarrhea (8.1% vs. 0%) were the only common AE more frequent in the pimecrolimus arm than vehicle arm. None of these was suspected to be treatment-related. Application site reactions occurred <5% for both arms. Rate of bacterial skin inection for pimecrolimus and vehicle: 0.8% vs. 6.3%	44 (23.7%) NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain Fair	Withdrawals due to AE were not reported. 20-week open-label extension was conducted in this trial (but was not abstracted because it does not meet inclusion criteria)

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	Double-blind, multicenter (41 centers) Randomization 4:1 (pimecrolimus: vehicle/conventional therapy)	3-23 mo with clinical diagnosis of atopic dermatitis according to criteria of Seymour, et al; affecting ≥5% of total BSA; IGA score of ≥2 Exclusion: phototherapy or systemic therapy known or suspected to affect AD ≤1 mo before the first application of study medication; topical therapy known or suspected to affect AD ≤7 days before the first application of study medication, and systemic antibiotics ≤2 weeks before the first application of study medication; were immunocompromised or had a history of malignant disease; had active skin infections; had other infections that required treatment with prohibited medications (ie, generally medication that could affect a patient's AD), and had other skin conditions that could affect the evaluation of study treatment.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	Pimecrolimus 1% cream vs. vehicle; applied twice daily x 12 mos; emollients were mandated and moderately potent topical steroids were allowed for flares not controlled by study medication. Topical steroids were to be administered until clearance or until the maximum treatment duration allowed by the local country label was reached. Treatment with corticosteroid was followed by a week of treatment with study medication for residual disease. Corticosteroids used were: 0.02% difluprednate cream, 0.1% hydrocortisone butyrate cream, 0.05% clobetasone butyrate cream, 0.02% triamcinolone acetonide cream, and 0.2% hydrocortisone valerate cream. Patients whose AD flares were not controlled by the topical corticosteroid could leave the study.	NR/NR	Nonmedicated emollients

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	Primary endpoint: rate of flares **at 6 mos** Secondary endpoints: IGA score, EASI score, caregiver's assessment of pruritus and overall assessment of disease control	11.8-12.2 mos Female 33.3-39.1% NR	Mean total BSA involved: 27.3-28.8% mean EASI: 12.3-12.6 IGA score: 1 (almost clear): 0% 2 (mild): 32.8-39.1% 3 (moderate): 47.8-57.4% 4 (severe): 8.3-10.9% 5 (very severe) 1.5-2.2%	280 251 251

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	69 14 250	% of patients without a flare for pimecrolimus and vehicle: At 6 mo: 67.6% (95% CI 61.2-74.1%) vs. 30.4% (95% CI 17.1-43.7%) At 12 mo: 56.9% (95% CI 50.1-63.7%) vs. 28.3% (95% CI 15.2-41.3%) % achieving IGA score of 0 to 1: At 6 mo: 52.9% vs. 37.0%, p=0.03 At 12 mo: 53.9% vs. 47.8%, p= NSD EASI mean total score: At 6 mo: 5.0 vs. 6.9, p=0.076 At 12 mo: 5.0 vs. 5.9, p=0.487 % with pruritus score of 0 or 1 (none or mild): At 6 mo: 73.0% vs. 54.4%, p=0.008 At 12 mo: 77.0% vs. 63.1%, p=0.074 % with complete of good control of disease as measured by caregiver: At 6 mo: 70.6% vs. 51.0%, p=0.016 At 12 mo: 71.0% vs. 63.0%, p=0.337

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	NR	Commonly reported AE for pimecrolimus and vehicle: Nasopharyngitis 56.9% vs. 46.2% Pyrexia 44.8% vs. 40.5% Teething 31.6% vs. 32.8% Diarrhea NOS 27.6% vs. 26.3% Upper respiratory tract infection NOS 27.3% vs. 25.3% Cough 26.0% vs. 16.5% Rhinitis NOS 24.0% vs. 15.8% Ear infection NOS 21.7% vs. 20.8% Chickenpox 19.6% vs. 15.6% Vomiting NOS 16.1% vs. 8.2% Otitis media NOS 14.9% vs. 15.5% Gastroenteritis NOS 14.8% vs. 14.9% Bronchitis NOS 14.6% vs. 16.2% Conjunctivitis NOS 13.9% vs. 13.9% Bacterial and viral skin infections: Total Bacterial 12.7% vs. 9.1% Impetigo NOS 9.1% vs. 6.8% Bacterial infection NOS 1.6% vs. 0% Folliculitis 0.5% vs. 0% Furuncle (exc genital) 0.5% vs. 0% Bacterial genital infection NOS 0.6% vs. 0% Stye 0.6% vs. 0% Erysipelas 0% vs. 2.3% Total Viral 3.3% vs. 6.9% Herpes simplex 1.1% vs. 3.4% Eczema herpeticum 0.5% vs. 0% Molluscum contagiosum 1.2% vs. 0% Skin papilloma 0.5% vs. 0% Viral rash NOS 0% vs. 3.4%	24.5% vs. 40.4%, p=0.016 NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Kapp, 2002 Europe, Canada, New Zealand, S. Africa Fair	Withdrawals due to AE were not reported

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Kaufmann, 2004 Germany Fair	Double-blind, multicenter (19 centers) Randomization 2:1 (pimecrolimus: vehicle)	3–23 mos if they had atopic eczema affecting ≥5% of the body surface area and a baseline IGA score of 2 (mild disease severity) to 5 (very severe disease). Exclusion: insufficient wash-out periods for systemic corticosteroids, antihistamines, antibiotics or other therapies that might have an effect on atopic eczema; concomitant diseases that might interfere with the study; severe concurrent skin disease in the study area, and active viral or bacterial infections.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Kaufmann, 2004 Germany Fair	Pimecrolimus 1% cream vs. vehicle; applied twice daily x 4 weeks.	NR/NR	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Kaufmann, 2004 Germany Fair	Primary endpoint: EASI score Secondary endpoint: IGA score, intensity of pruritus/sleep loss and overall assessment of disease assessed by the caregivers (using part of SCORAD)	11.5-12.3 mo (SD 5.8-6.1) Female 28.8-37.2% White 90.7-92.4% Black 0-1.6% Asian 5.4-6.1% Other 1.5-2.3%	Height 74.4-75.3 cm (SD 7.2-8.0) Weight 9.4 kg (SD 2.0-2.1) IGA score 2 (mild): 9.3-12.1% 3 (moderate): 58.1-59.1% 4 (severe): 25.8-26.4% 5 (very severe): 3.0-6.2% EASI score: 16.6-17.7 (SD 10.3-10.8) IGA score: 3.2-3.3 (SD 0.7) SCORAD score: 46.9-48.6 (SD 15.0-15.9)	201 NR 196

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Kaufmann, 2004 Germany Fair	38 NR 195	Mean EASI score for pimecrolimus and vehicle: Score at 4 weeks: -4.9 (SD 6.0) vs. +17.3 (SD 13.3) % decrease in score from baseline: -71.5% vs. +19.4%, p<0.001 vs. vehicle % achieving IGA score of 0 to 1 (treatment success): 53.5% vs. 10.6%; p<0.001 for between-group comparison) Caregiver's assessment of disease response as "good or complete": 80.6% vs. 22.7%, p<0.001 vs. vehicle Mean pruritus score: Score at 4 weeks: 2.1 (SD 2.3) vs. +5.2 (SD 3.3), p<0.001 vs. vehicle Mean sleep loss score: Score at 4 weeks: 1.6 (SD 2.3) vs. +4.1 (SD 3.3), p<0.001 vs. vehicle

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Kaufmann, 2004 Germany Fair	NR	3 patients discontinued due to serious AE: 1-patient from pimecrolimus arm discontinued due to moderate case of eczema herpeticum; 1 pimecrolimus-treated and 1- vehicle patient experienced super infection on top of aggravated AD. Most common AE were typical childhood ailments (see Table 2 in trial). There was no difference in treatment arms after adjusting for time.	38 (19.4%) NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Kaufmann, 2004 Germany Fair	Authors did not specify total # of withdrawals due to AE (they reported the withdrawal of 3 patients due to serious AE)

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Meurer, 2002 Germany Fair	Double-blind, multicenter (16 sites)	Adults with a clinical diagnosis of AD according to the criteria of Rajka; required to have AD affecting at least 5% of the total body surface area; an Investigator's Global Assessment (IGA) score of 3 or 4. Exclusion: PUVA, high-dose UVA or systemic therapy with corticosteroids, immunosuppressants or cytostatics (previous 3 months); topical therapies for AD (previous 2 weeks); systemic antibiotics (previous 2 weeks); systemic steroids for indications other than AD (previous 1 month). Other exclusion criteria comprised: pregnancy or lactation; women of child-bearing age not using reliable contraception; need for treatment with potent topical steroids for control of AD; severe concurrent allergic diseases; diseases associated with immunosuppression or malignancy; presence of skin conditions that could affect the evaluation of study treatment; active skin infections requiring treatment with a prohibited medication, or active herpes simplex infections.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Meurer, 2002 Germany Fair	Pimecrolimus 1% cream vs. vehicle; applied twice daily in order to prevent disease flare x 6 mos Nonmedicated emollients were applied to dry skin after study medication. A moderatley potent topical steroid, prednicarbate 0.25% cream if the patient experienced unacceptable itcing and clinical signs (oozing/crusting or excessive scratch marks or severe erythema) despite study medication. Topical steroid was to be used for a max of 7 days twice daily followed by a further 7 days every other day or until marked reduction of the signs of AD were achieved. After each course of sterid there was a mandaory treatment for 7 days with the study drug.	NR/NR	Nonmedicated emollients and cetirizine.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Meurer, 2002 Germany Fair	Primary endpoint: % of days on topical steroids (to assess pimecrolimus in preventing disease flares) Secondary endpoint: # of flares, time to 1st flare, IGA score, EASI score, pruritus assessment, patient's self-assessment, DLQI QoLIAD Baseline, weeks 1, 3, 6, 12, and 24. There was additional telephone contact during weeks 9 and 18 and unscheduled visits in the event of flares.	31.8-32.5 (SD 10.7-11.1) Female 57.3-62.5% NR	Total BSA involved: mean 16.9-17.0% (SD 7.6-10.7) mean EASI: 10.8-11.2 (SD 5.1-6.1) IGA score: 3 (moderate): 64.6-70.8% 4 (severe): 29.2-34.4% 5 (very severe): 0.0-1.0%	197 192 192

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Meurer, 2002 Germany Fair	58 4 192	% of days of topical steroid for pimecrolimus and vehicle: All patients: (mean) 14.2% (SD 24.2) vs. 37.2% (SD 34.6), p<0.001 All patients: (median) 2.1% vs. 27.8% For those with moderate disease: (mean) 9.5% (SD 19.8) vs. 37.0% (SD 36.3), p<0.001 For those with moderate diseae: (median) 0.0% vs. 23.5% For those with severe disease (IGA 4): (mean) 23.1% (SD 29.5) vs. 37.8 (SD 30.4), p=0.027 For those with severe disease: (median) 7.7% vs. 35.2% % of patients with no steroid use: 49% vs. 21.9% Mean # of flares at study end: 1.1 flares (95% CI 0.7-1.4) vs. 2.4 (95% CI 2.0-2.8), p<0.001 vs. vehicle % of patients with no flare at study end: 44.8% vs. 18.8% % of patients classified as treatment success per IGA score of ≤2: 68.6% vs. 36.5%, p-value=NR Patient's self assessment of their disease as completely or well-controlled: 64.6% vs. 35.4%, p-value=NR Pruritus score at week 24: not reported; scores from day 1-7 were reported instead (see Fig 4 in trial) % EASI score declined from baseline: 48.3% vs. 15.9%, p<0.001

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Meurer, 2002 Germany Fair	NR	Five patients discontinued due to AE (1 patient in the pimecrolimus arm had an aneurysm, which was not suspected to be study drug-related; 3 patients in the vehicle arm had contact dermatitis and 1 had application site reaction). 10 pimecrolimus-treated patients vs. 3-vehicle treated patients experienced application site burning which resolved within 1-7 days. 18.8% vs. 9.4% of pimecrolimus-and vehicle-treated patients had at least 1 skin infection by month 6 (95% CI -19.1 to 0.4). This was mainly due to higher herpes infection rates in the pimecrolimus than vehicle arms (10 vs. 5) whereas the rates of bacterial (4 vs. 3) and fungal (2 vs. 1) infections were similar. 6 of 10 cases in the pimecrolimus arm were due to herpes labialis (areas not treated with study medication) compared with 1 of 5 in the vehicle arm. There were 2 cases of eczema herpeticum in the vehicle group. (No other AE data were reported)	58 (30.2%) 5

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Meurer, 2002 Germany Fair	Pruritus score at the end of study were not reported. Authors did not report what type of herpes infections occurred for the remaining 4 patients in the pimecrolimus arm or the remaining 2 patients in the vehicle arm.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	Double-blind, multicenter (16 sites)	Adults with a clinical diagnosis of AD according to the criteria of Rajka; required to have AD affecting at least 5% of the total body surface area; patient's with an Investigator's Global Assessment (IGA) score of 3 were included for this analysis. Exclusion: PUVA, high-dose UVA or systemic therapy with corticosteroids, immunosuppressants or cytostatics (previous 3 months); topical therapies for AD (previous 2 weeks); systemic antibiotics (previous 2 weeks); systemic steroids for indications other than AD (previous 1 month). Other exclusion criteria comprised: pregnancy or lactation; women of child-bearing age not using reliable contraception; need for treatment with potent topical steroids for control of AD; severe concurrent allergic diseases; diseases associated with immunosuppression or malignancy; presence of skin conditions that could affect the evaluation of study treatment; active skin infections requiring treatment with a prohibited medication, or active herpes simplex infections.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	Pimecrolimus 1% cream vs. vehicle; applied twice daily in order to prevent disease flare x 6 mos Nonmedicated emollients were applied to dry skin after study medication. A moderatley potent topical steroid, prednicarbate 0.25% cream if the patient experienced unacceptable itcing and clinical signs (oozing/crusting or excessive scratch marks or severe erythema) despite study medication. Topical steroid was to be used for a max of 7 days twice daily followed by a further 7 days every other day or until marked reduction of the signs of AD were achieved. After each course of sterid there was a mandaory treatment for 7 days with the study drug.	NR/NR	Nonmedicated emollients and cetirizine.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	Primary endpoint: % of days on topical steroids (to assess pimecrolimus in preventing disease flares) Secondary endpoint: # of flares, time to 1st flare, IGA score, EASI score, pruritus assessment, patient's self-assessment, DLQI QoLIAD Baseline, weeks 1, 3, 6, 12, and 24. There was additional telephone contact during weeks 9 and 18 and unscheduled visits in the event of flares.	29.2-31.4 (SD 9.7-10.0) Female 59.7-63.2% White 97.9-100%	Total BSA involved: mean 12.7-13.9% (SD 5.8) mean EASI: 8.6-9.3 (SD 3.9-4.0) IGA score: 3 (moderate): 64.6-70.8% 4 (severe): 29.2-34.4% 5 (very severe): 0.0-1.0%	197 192 192 130 (had moderate disease)

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	32 NR 130	% of days of topical steroid for pimecrolimus and vehicle: 9.7% vs. 37.8%, p<0.001 % of patients with no steroid use: 59.7% vs. 25% Mean # of flares at study end: 1.0 flares (SD 1.5) vs. 2.3 (SD 2.5), p<0.001 % of patients with no flare at study end: 59.7% vs. 22.1%, p<0.001 % of patients classified as treatment success per IGA score of ≤2: 80.6% vs. 36.8%, p<0.001 Patient's self assessment of their disease as completely or well-controlled: 72.6% vs.38.2%, p<0.001 % decrease in pruritus score at week 24: 69.3% vs. 35.3%, p<0.001 % EASI score declined from baseline: 71.1% vs. 11.6% Raw scores for pimecrolimus: from 8.8 to 2.1 Raw scores for vehicle: from 8.5 to 5.2 Mean decrease (ie, improvement) in QoLIAD score: 34.9% vs. 10.5% Mean decrease (ie, improvement) in DLQI score: 22.9% vs. 0.9% Data were not shown

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	NR	No patients in the pimecrolimus group and only 3 patients in the vehicle arm withdrew due to AE. Local application site reactions were the most common AE: 14.5% pimecrolimus vs. 8.8% vehicle arm. A total of 21.0% of pimecrolimus and 11.8% vehicle-treated patients experienced skin infections during the study. Herpes simplex infection occurred in 11.3% pimecrolimus vs. 4.4% vehicle. Table 3 in the trial provides more detail of AE.	32 (24.6%) 3

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Meurer, 2004 Germany companion to Meurer, 2002 (only patients with moderate disease were included in this analysis)	

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Siegfried, 2006 US Fair	Double-blind, multicenter (35 centers) Randomized 2:1 (pimecrolimus: vehicle)	3 mos-11 yrs with mild to severe AD; at least 5% of total BSA; AD diagnosed using Sampson's criteria for subjects <2 yrs and Williams' criteria for > 2 yrs; AD severity determined using Investigator's Global Assessment (IGA). Exclusion criteria were immunocompromised children; those with a concurrent skin disease that could interfere with evaluations; patients with AD triggered by a known, unavoidable allergen or irritant; and those with an active viral or bacterial infection. Excluded therapies for the duration of the study were all topical and systemic agents known or thought to be effective in treating AD, including sedating antihistamines.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Siegfried, 2006 US Fair	Pimecrolimus 1% cream versus vehicle' applied twice daily x 6 months. After 7 days, if the AD had not improved or had worsened to the point at which the investigator judged it was severe (IGA>4), a major flare regimen was introduced. In this flare regimen, the evening study drug dose was replaced with a mid-potency topical CS with demonstrated once-daily (qd) efficacy in AD. Rescue steroids for major flare-ups: fluticasone propionate 0.05% cream for all patients and mometasone furoate 0.1% cream for subjects >2 yrs x 3 weeks maximum. A mandatory 7-day CS-free period must have elapsed before another 3 weeks of the flare regimen could be started. The subject or caregiver was contacted by telephone each week during periods of the major flare to monitor compliance, flare duration, and steroid use.	Run-in: NR Washout: 1-month for systemic anti-inflammatory agents or phototherapy; 1-week for all topical agents except low-or mid-potency steroids; 2-week for all systemic antibiotics	Nonmedicated emollients

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Siegfried, 2006 US Fair	IGA, EASI, pruritus severity score (4-point scale). IGA and EASI scores recorded weekly x 1st month then monthly to the end of the study (at 6 months). Pruritus score recorded daily on diary cards for 1st 3 weeks. Primary endpoint: % of patients with no major flares over 6 months. Definition of flare: after 7 days, if the AD had not improved or had worsened to the point at which the investigator judged it was severe (IGA>4), a major flare regimen was introduced. Secondary endpoints: # of days of steroid use; change in EASI score; daily pruritus score; # of major flares over 24-weeks; # of days to onset of 1st flare; # of days between 1st and 2nd flare; time to reach pruritus score improvement by at least 1 point	59.9 (SD 38.98) NR NR	IGA mean score: 2.9 (moderate severity) Pruritus severity score (mean): 1.9 Total body surface area affected: 29%	NR NR 275

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Siegfried, 2006 US Fair	59 20 272 (98.9%)	% of those with no single major flare x 6 mos for pimecrolimus and vehicle: 51.9% vs. 34.1%, p=0.007 % of those with at least 1 major flare x 6 mos: 40.3% vs. 56%, p= NR % of those with > 2 major flares x 6 mos: 7% vs. 23%, p= NR # of days to onset of first major flare (median): 53 days vs. 13 days, p<0.001 between groups # of days between first and second major flares (median): 31 days vs. 15 days, p=0.003 # of days of topical steroid use (mean): 10.9 days vs. 17.3 days, p=0.002 EASI score at 6 mos: NR IGA scores at 6 mos: NR EASI and IGA scores were reported for day 8 instead (see study) The difference in EASI and IGA narrowed over time and lost significance, subsequent to introduction of topical steroid.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Siegfried, 2006 US Fair	Did not report who assessed AE; confirmatory viral culture for all suspected cases of eczema herpeticum were taken	AE were similar in overall incidence and type. Most AE represented typical childhood illnesses. There was no statistically significant between-treatment difference by crude incidence or time-adjusted analysis except for rhinorrhea (pime 9.8% vs. 2.2% vehicle, p=0.025). AE types: diarrhea, vomiting, ear infection NOS, impetigo, otitis media NOS, upper respiratory tract infection, pyrexia, cough, nasal congestion, nasopharyngitis, rhinorrhea The most common suspected drug-related AE: application site reaction in 2.2% in each arm) 1-case of impetigo in pime arm was considered severe; no cases of eczema herpeticum were reported in either arm; crude incidence of each type of skin infection was usually <2% and none showed statistically significant between-treatment difference.	59 (Pime:28%, Vehicle: 18%) NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Siegfried, 2006 US Fair	Withdrawals due to AE were not reported; EASI and IGA scores at end of the study were not reported

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Staab, 2005 Germany companion to Kaufmann, 2004	same as Kaufmann, 2004	same as Kaufmann, 2004	same as Kaufmann, 2004

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Staab, 2005 Germany companion to Kaufmann, 2004	same as Kaufmann, 2004	same as Kaufmann, 2004	same as Kaufmann, 2004

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Staab, 2005 Germany companion to Kaufmann, 2004	In addition to the above outcomes: Parent's QoL was measured at baseline and at 4 weeks using the PQoL-AD (different from PIQoL-AD) and % change in SCORAD index was reported for this paper.	same as Kaufmann, 2004	same as Kaufmann, 2004	same as Kaufmann, 2004

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Staab, 2005 Germany	same as Kaufmann, 2004	Mean % change from baseline in SCORAD index for pimecrolimus and vehicle: -55.2% vs. +1.1%, p=0.002
companion to Kaufmann, 2004		Mean % change from baseline: all 5 domains, p<0.05 vs. vehicle Most notable were: Psychosomatic well-being: 14.6% change vs. 6.22% Emotional coping: 16.1% vs. 6.5% Acceptance of disease: 19.6% vs. 6.98% Analysis of the relationship between various scoring methods (IGA, EASI, SCORAD) and QoL showed weak correlations.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Staab, 2005 Germany companion to Kaufmann, 2004	NR	Not primary focus. Data were not shown. Authors only report that parent's reports of application site reactions were rare, occurring in only 1-patient in each group.	same as Kaufmann, 2004

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Staab, 2005 Germany companion to Kaufmann, 2004	

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Van Leent, 1998 Netherlands Fair	Double-blind, single-center (proof of concept)	All patients had AD according to the criteria of Hanifin and Rajka with at least 1% of the body surface area affected on both arms. For assessment of severity of the dermatitis weused the Atopic Dermatitis Severity Index (ADSI). Exclusion criteria were as follows: patients receiving radiation therapy, systemic therapy with cytostatics, or immunosuppressive drugs within 24 weeks before randomization; receiving phototherapy or systemic therapy for AD within 1 month before randomization; receiving antibiotics or topical therapy for AD within 2 weeks before randomization (however, the once-daily use of 1% hydrocortisone acetate was allowed on all lesions with the exception of the test sides selected for the study, and emollients were allowed to be used liberally but not on the test sides); taking antihistamines within 1 week before randomization; and acute skin infection (superinfection) at randomization.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Van Leent, 1998 Netherlands Fair	Pimecrolimus 1% cream vs. vehicle; applied twice daily or once daily; applied to either the left arm or right arm x 3 weeks.	NR/NR	Hydrocortisone acetate 1% on all other leisons except the study specific ones

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Van Leent, 1998 Netherlands Fair	ADIS scoring method Baseline, days 4, 11, 21	29.1-35.8 (SD 13.2-13.7) 43.7-61.1% NR	Mean ADSI score for pimecrolimus and vehicle: Twice daily arm: 8.1 (SD 1.2-1.4) Once daily arm: 7.7-7.8 (SD 1.2-1.3)	38 NR 34

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Van Leent, 1998 Netherlands Fair	7 NR 34	For twice daily dosing arm: Mean % change in ADSI score from baseline for pimecrolimus and vehicle: 71.9% vs. 10.3%, p<0.001 For once daily dosing arm: Mean % change in ADSI score from baseline: 37.7% vs. 6.2%

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Van Leent, 1998 Netherlands Fair	NR	Detailed report of AE were not reported. Authors state that "no skin irritations or any other local adverse events were observed. No relevant changes were observed in the patients' lab test values…all vital signs and results of physical examinations were normal. There were no clinically signficant adverse effects (ie, drug-related adverse events)."	7 NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Van Leent, 1998 Netherlands Fair	

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	Double-blind, multicenter (53 centers) Randomization 2:1 (pimecrolimus:vehicle)	2-17 yrs; had a diagnosis of AD according to the criteria of Williams et al; AD affecting at least 5% of total body surface area and an Investigators' Global Assessment (IGA) score of ≥2. Excluded if they had received phototherapy or systemic therapy known or suspected to affect AD up to 1 month before the first application of study medication, topical therapy known or suspected to affect AD up to 7 days before the first application of study medication, or systemic antibiotics up to 2 weeks before the first application of study medication. Also excluded were patients who had infections that required treatment with prohibited medications (ie, generally medication that could affect a patient's AD) or skin conditions that could affect the evaluation of study treatment.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	Pimecrolimus 1% cream vs. vehicle; applied twice daily x 12 mos; emollients were mandated and moderately potent topical steroids were allowed for flares not controlled by study medication. Topical steroids were to be administered until clearance or until the maximum treatment duration allowed by the local country label was reached. Treatment with corticosteroid was followed by a week of treatment with study medication for residual disease. Corticosteroids used were: 0.02% difluprednate cream, 0.25% prednicarbate cream, 0.1% hydrocortisone butyrate cream, 0.05% clobetasone butyrate cream, 0.02% triamcinolone acetonide cream, and 0.2% hydrocortisone valerate cream.	NR/NR	Antihistamines/H1 blockers if stable dose throughout study could be ensured

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	Primary endpoint: rate of flares at **6 mos** Secondary endpoints: rate of flares at 12 mos, IGA score, EASI score	7.9-8.0 yrs Female 52.7% NR	mean EASI: 13.3-13.8 % of mean total BSA affected: 23.8-24.2% IGA score: 1 (almost clear): 0-0.2% 2 (mild): 26.2-27.8% 3 (moderate): 50.6-55.3% 4 (severe) 15.6-17.7% 5 (very sever) 2.7-3.8% Note: 1 patient had an IGA score of 1 at baseline; however, this patient had a baseline EASI score >10 (ie, mild-moderate disease)	733 713 713

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	272 (38.1%) 22 711 (99.7%)	% of patients without a flare for pimecrolimus and vehicle: At 6 mo: 61.0% vs. 34.2% At 12 mo: 50.8% vs. 28.3% % achieving IGA score of 0 to 1: not reported (Authors report that the results were similar to EASI scores) % reduction in median EASI score: (data not reported; estimated from graph) approx -61% vs. approx -39% Outcomes that were not prespecified in the methods but were reported in the results section were: the % requiring steroids, % of days on steroids (see study for more details)

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	NR	Most frequent AE were common childhood infections and ailments such as: nasopharyngitis, headache, bronchitis, influenza, cough, pyrexia, application site burning (10.5% pimecrolimus vs. 9.3% vehcile). The authors reported AE with ≥10% incidence (see Table 3 in study for more details). There was slightly greater incidence of viral skin infections in the pimecrolimus- than vehicle arm (total rate: 12.4% vs. 6.3%, p=0.038; see Table 4 in study for more details). 10 patients in pimecrolimus arm vs. 2 patients in the vehicle arm had eczema herpeticum.	272 NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Wahn, 2002 europe, US, Canada, S. Africa, Austrailia Fair	IGA scores were not reported and other unprespecified outcomes were reported. Withdrawals due to AE were not reported.

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Zuberbier, 2007 Germany Fair	Double-blind, multicenter (22 dermatologic and pediatric centers)	2-17 yrs; history of severe AD determined by score of 8 or 9 in the Rajka and Langeland grading; in cases of active symptoms those who responded to prednicarbate cream 0.25% (max 21 day therapy) during the screening phase were eligible. Those who received topical steroids within 7 days or phototherapy or systemic corticosteroids /immunosuppressantswithin 1 month prior to study entry were excluded; children with active acute viral infection or those who were immunocompromised were also excluded.	NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Zuberbier, 2007 Germany Fair	Pimecrolimus 1% cream or vehicle; applied twice daily x 24 weeks For flare-up, treatment with prednicarbate cream (topical steroid) 0.25% was reinstated twice per day in place of pimecrolimus cream till flare was controlled. In case of a flare, treatment with prednicarbate cream was reinitiated by the patient instead of treatment with the study medication. Once flare was controlled, topical steroid was discontinued and study medication was resumed.	Run in: during in screening phase, patients were treated with prednicarbate 0.25% for at least 7 days (max 21 days). If there was no significant improvement after 21 dyas, patient was not eligible. Washout: none. Patients were switched from prednicarbate cream to the study medication for at least 7 days.	Nonmedicated emollients

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Zuberbier, 2007 Germany Fair	Primary endpoint: was the need for topical steroid during the time between randomization and the end of the study. This was measured as the % of days on which pateints decided to use topical steroids instead of study medication. Secondary endpoints: EASI score, the patient's overall self assessment scores, QOL measured at screening, 6 weeks of treatment and end of study using Children's Dermatological Life Quality Index, and Parents Index of quality of Life-AD	7.6 (SD 4.9), Female 52% White 93% Black 1% Asian 5% Other 1%	Rajka and Langeland score at screening : 8.3 IGA scores 3 (moderate disease): 39% 4 (severe disease): 42% 5 (very severe disease): 6%	195 NR 184

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Zuberbier, 2007 Germany Fair	29 NR NR	% of days that patients required additional steroids for pimecrolimus vs. vehicle: 29% of days (SD 25) vs. 35% of days (SD 25), (absolute difference 6%; 95% CI 11.8 to -2.3%, p=0.1841) EASI score: 7 (SD 6) vs. 9 (SD 8), p=0.0827 Patient's Overall Self Assessment score: not reported Parent's QoL (mean score) at week 24: 4.2 (SD 5.2) vs. 6.2 (SD 5.9) Between-group difference: -2.0, p=0.047 Patient's (mean score) QoL at week 24: 3.6 (SD 3.7) vs. 4.6 (SD 4.6), p=0.225 Subgroup % of days that patients required additional steroids for pimecrolimus vs. vehicle (for head/neck): 10% of days (SD 14) vs. 19% of days (SD 22), (95% CI 14.1 to 3.7%, p=0.0009) % of days for the rest of the body 27% of days (SD 25) vs. 30% (SD 24), p=0.64 For subgroup with IGA score of 4 or 5 (severe to very severe disease): % of days of steroid application: 28% of days (SD 21) vs. 45% (SD 27), (absolute difference 17%; 95% CI 24.8 to 5.6%, p=0.0024) Mean EASI score: 9 (SD 7) vs 13 (SD 10), p=0.0041 Patient's overall self-assessment score: 2.3 (SD 0.7) vs. 2. (SD 0.9), absolute difference -0.4; p=0.029

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Zuberbier, 2007 Germany Fair	Did not report who assessed AE; patient and caregiver interviews were conducted and diary cards were utilized	5 AE with suspected drug relationship occurred in 5 pimecrolimus-treated subjects compared with 10 AE in 4 vehicle-treated subjects. 1-patient randomized t vehicle had 6 allergic eye disorders. 2 patients on pimecrolimus reported application site reaction compared wit 1 patient (did not report how often these reactions occurred nor the types of reactions that were observed).	29/ NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Zuberbier, 2007 Germany Fair	Rajka and Langeland scores did not corelate closely with active severe disease. 48% had severe to very severe AD at screening (IGA score of 4 and 5). Patient's overall self-assessment score for the entire population was not reported. It was selectively reported for the subgroup analysis. Withdrawals due to AE were not reported

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Eichenfield, 2002 US Fair	Double-blind, multicenter This pooled study includes data from 2 larger unpublished trials. Both trials were of identical study design. These 2 trials were later identified in the FDA dossier as study #305 and #307.	1-17 yrs; AD diagnostic criteria of Williams et al; AD affecting at least 5% of total body surface area (TBSA); an Investigator's Global Assessment (IGA) score of 2 or 3, corresponding to mild to moderate disease; and receiving stable doses of an additive-free, basic bland emollient for at least 7 days before baseline (day 1). Reasons for exclusion: pregnancy or nursing; phototherapy (eg, UVB, PUVA) or systemic therapy (eg, immunosuppressants, cytostatics) for AD within 1 month, or topical therapy (eg, tar, topical corticosteroids) within 7 days before the first application of study medication; systemic antibiotics in the 2 weeks before the first application of study medication; and significant concurrent disease.	NR
Study #305 (From FDA reviews)	see above	see above	see above

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Eichenfield, 2002 US Fair	Pimecrolimus 1% cream, vehicle cream; applied twice daily x 6 weeks 2: 1 randomization	NR/NR	Bland emollients
Study #305 (From FDA reviews)	see above	see above	see above

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Eichenfield, 2002 US Fair	IGA score ≤1, EASI, patient assessment of pruritus (score system), patient assessment of overall disease control Baseline, and on days 8, 15, 22, 29, and 43.	Pooled results: 6.6-6.8 yrs Female 47.6-54.4% White 48.5-54.7% Non-white: 45.3-51.5%	IGA Mild 30.0-31.6% Moderate 57.4-60.3% Severe 8.1-8.6% Very severe 1.1-2.9% %TBSA 25.5-26.1% Mean EASI: 12.7-12.9	Pooled NR NR 403
Study #305 (From FDA reviews)	see above	6.4-6.9 yrs Female 48.5-51.5% White 50.0-58..5% Black 14.6-17.6% Asian 10.0-11.8% Other 16.9-20.6%	Weight 27.9-28.9 kg Height 117.5-121.4 cm IGA score Mild 21.5-26.5% Moderate 55.9-63.8% Severe 11.8-12.3% Very severe 2.3-5.9% % TBSA: 27.4-29.7%	219 NR 198

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Eichenfield, 2002 US Fair	Pooled 64 (15.8%) NR 403 NR	Pooled: Reported as pimecrolimus vs. vehicle % achieving IGA score ≤1: 34.8% vs. 18.4%, p≤0.05 % improvement in EASI score: -45% vs. -1%, p≤0.001 Actual data not reported for patients who reported mild or no pruritus. Authors report that more pimecrolimus-treated patients reported mild-no pruritus than placebo-treated patients. Data at day 43 were not provided for both treatment arms. An estimate based on figure 4: 56% vs. 35%, p<0.001 Actual data not reported for % of patients reporting good or complete control of their disease. An estimate from Figure 5 (3-dimensional bar graph): 60% vs. 40%, p<0.05
Study #305 (From FDA reviews)	36 (18.2%) 6 (3%) 198	For pimecrolimus vs. vehicle: IGA score ≤1: 37.7% vs. 16.2%, p=0.002 Frequency of pruritus score: Score of 0 (absence of itch): 13.8% vs. 0.0%, p=0.001 Score of 1 (mild presence of itch): 36.2% vs. 32.4%, p=NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Eichenfield, 2002 US Fair	NR	For pimecrolimus vs. vehicle: Application site burning: 10.4% vs. 12.5% Nasopharyngitis: 10.1% vs. 7.4% Cough 11.6% vs. 8.1% Headache NOS 13.9% vs. 8.8% Upper respiratory tract infection 14.2% vs. 13.2%	64 (15.8%) 9 (2.2%)
Study #305 (From FDA reviews)	see above	see above	12.3% vs. 29.4% (total 18.2%) NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Eichenfield, 2002 US Fair	
Study #305 (From FDA reviews)	Primary reason for withdrawal lack of efficacy 4.6% vs. 23.5% (total 11.1%), p=0.001

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, immunodeficiencies)?
Study #307 (From FDA reviews)	see above	see above	see above

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Study #307 (From FDA reviews)	see above	see above	see above

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Study #307 (From FDA reviews)	see above	6.7-6.9 yrs Female 43.8-60.7% White 47.1-51.1% Black 27.7-33.8% Asian 1.5-3.6% Other 17.5%	Weight 30.2-31.3 kg Height 121.7-123.5 cm IGA score Mild 36.8-38% Moderate 56.9-58.8% Severe 4.4-5.1% %TBSA 22.7-23.6	272 NR 205

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)
Study #307 (From FDA reviews)	28 (13.7%) 8 (3.9%) 205	For pimecrolimus vs. vehicle: IGA score ≤1: 32.1% vs. 20.6%, p=0.076 (NSD) Frequency of pruritus score: Score of 0: 17.5% vs. 4.4%, p=0.009 Score of 1: 45.3% vs. 30.9%, p=NR

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse events	Total withdrawals; withdrawals due to adverse events
Study #307 (From FDA reviews)	see above	see above	10.2% vs. 20.6% (total 13.7%), p=0.047 2.2% vs. 2.9% (total 2.4%), p=NSD

Evidence Table 5. Placebo-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Comments
Study #307 (From FDA reviews)	Primary reason for DC was unsatisfactory therapeutic effect: 0.7% vs. 7.4% (total 2.9%)

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Siegfried, 2006 US	Method not described	Method not described	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes, corresponding vehicle was identical in appearance to active arm
Zuberbier, 2007 Germany	Yes, automated random assignment via random number	Yes, automated number assignment	Yes	Yes	Yes	Yes	Yes
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain	Method not described	Method not described	Yes (except there were slightly more Black patients randomized to pimecrolimus)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Belsito, 2004 US	Method not described	Method not described	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Kaufmann, 2004 Germany	Yes, computer generated randomization list	Yes	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Siegfried, 2006 US	Yes NR NR NR	Yes, differential (18% for pimecrolimus vs. 28.3% vehicle) Yes (21.5% total)	Yes, unclear how missing data were handled	No	Fair	Novartis
Zuberbier, 2007 Germany	Yes NR NR NR	Yes, differential (12% for pimecrolimus vs. 20% vehicle) No (assuming true ITT 15.8%)	Unable to verify if truly ITT and unclear how missing data were handled	No	Fair	Novartis
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain	Yes NR NR NR	Yes, differential (11.4% pimecrolimus vs. 47.6% vehicle) Yes (23.7% total)	Yes with LOCF	No	Fair	Novartis
Belsito, 2004 US	Yes NR NR NR	No/No (7.5% total)	Yes with LOCF	No	Fair	Novartis
Kaufmann, 2004 Germany	Yes NR NR NR	Yes, differential (10% pimecrolimus vs. 37.9% vehicle) No (19.4% total)	Yes with LOCF	No	Fair	Novartis

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Comments
Siegfried, 2006 US	Did not specify the withdrawal rate from AE for each arm
Zuberbier, 2007 Germany	Did not report LTFU, withdrawals due to AE for each arm
Ho, 2003 Austrailia, Brazil, Canada, Germany, S. Africa, Spain	Did not report withdrawals due to AE for each arm
Belsito, 2004 US	
Kaufmann, 2004 Germany	

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kapp, 2002 Europe, Canada, New Zealand, S. Africa	Method not described	Method not described	No, control arm had slightly more patients with severe to very severe disease while pimecrolimus arm had slightly more patients with moderate disease	Yes	Yes	Yes	Yes
Meurer, 2002 Germany	Yes, computer generated randomization list	Yes	Yes	Yes	Yes	Yes	Yes
Wahn, 2002 Europe, US, Canada, S. Africa, Austrailia	Yes, automated random assignment via random number	Yes	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Van Leent, 1998 Netherlands	Method not described	Method not described	No, >15% more females were randomized to once daily dosing arm	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind
Luger, 2001	Method not described	Method not described	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Kapp, 2002 Europe, Canada, New Zealand, S. Africa	Yes NR NR NR	Yes, differential (24.5% pimecrolimus vs. 40.4% vehicle) Yes (27.5% total)	Yes, missing primary endpoint data were ranked; missing secondary endpoint data were LOCF	No	Fair	Novartis
Meurer, 2002 Germany	Yes NR NR NR	Yes, differential (22.9% pimecrolimus vs. 37.5% vehicle) Yes (30.2% total)	Yes with LOCF	No	Fair	Novartis
Wahn, 2002 Europe, US, Canada, S. Africa, Austrailia	Yes NR NR NR	Yes, differential (31.6% pimecrolimus vs. 51.5% vehicle) Yes (38.1% total)	Yes, missing primary endpoint data were ranked; unclear how missing data for secondary endpoints were handled	No	Fair	Novartis
Van Leent, 1998 Netherlands	Yes NR NR NR	Yes, differential (12.5% BID-dosing arm vs. 27.9% Qdaily dosing arm) Yes (20.6% total)	Yes but unclear how missing data were handled	No	Fair	Novartis
Luger, 2001	Yes NR NR NR	29 Yes, there was high differential seen with those randomized to vehicle compared with the other arms	Yes; unclear how missing data were handled	No	Fair	NR

Evidence Table 6. Quality assessment of placebo-controlled trials of pimecrolimus

Author, Year Country	Comments
Kapp, 2002 Europe, Canada, New Zealand, S. Africa	
Meurer, 2002 Germany	Defined treatment success as having IGA score ≥2 which is different from other trials that use score ≤1.
Wahn, 2002 Europe, US, Canada, S. Africa, Austrailia	
Van Leent, 1998 Netherlands	
Luger, 2001	

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Ruzicka, 1997 Europe European Tacrolimus Mutlicenter Atopic Dermatitis Study Group Fair	Double-blind, multicenter in Europe	13-60 years, with a confirmed diagnosis of moderate-to-severe atopic dermatitis, according to the criteria of Rajka and Langeland. Patients were excluded if they had received any therapy for atopic dermatitis, other than emollients or antihistamines, within 3 wks before the start of the washout phase. The criteria for entry into the treatment phase were a symptomatic area of at least 200 cm^2 of skin on the trunk or extremities or both, and no evidence of hypersensitivity to the ointment base (tested by daily application during the washout phase). At the start of the treatment phase, 200-1000 cm^2 of affected skin was selected for treatment. The affected area could be noncontiguous and could include the trunk, extremities, face, and neck, but at least 200 cm^ 2 had to be on the trunk or extremities. Investigators were instructed to select the lesions with the worst erythema and edema.	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Ruzicka, 1997 Europe European Tacrolimus Mutlicenter Atopic Dermatitis Study Group Fair	Tacrolimus 0.03-, 0.1-, or 0.3% ointment applied twice daily versus vehicle-alone (ointment based) x 3 weeks	NR/NR	No concurrent treatment other than emollients or bath oils were allowed

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Ruzicka, 1997 Europe European Tacrolimus Mutlicenter Atopic Dermatitis Study Group Fair	Investigator graded the area of treatment, on a scale of 0-3, for for the severity of erythema, edema, oozing or crusting, excoriation, and lichenification of all involved skin and dryness of noninvolved skin. Patients graded the puritus on a 10-cm visual analogue scale. An overall assessment of the condition of the treated area (symptoms completely resolved, markedly improved, moderately improved, slightly improved, unchanged, or worse) were performed by both the investigator and patient.	27-30 (SD 9-12) Female 52-69% White 94-98%	Mean total-body involvement: Trunk/extremities: 3367-3848 (SD 3654-4361) cm^2 Face/neck: 307-404 (SD 327-364) Median total-body score: 13.0-14.0 (reference 0-24) *this score includes sleep loss Area selected for treatment: Mean area 778-821 (SD 254-273) cm^2 Median score 1: 6.0 (reference 0-9)	250 NR 215

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Ruzicka, 1997 Europe European Tacrolimus Mutlicenter Atopic Dermatitis Study Group Fair	42 NR 213	Score 1: median percent change for tacrolimus 0.03-, 0.1-, 0.3%: Trunk/extremities: 66.7%, 83.3%, 75.0% versus vehicle: 22.5%, p<0.001 from baseline Face/neck: 71.4%, 83.3%, 83.3% versus vehicle: 25.0%, p<0.001 from baseline An ANOVA with pairwise comparisons showed no significant differences among the different tacrolimus doses. Score 2: median percent change for 0.03-, 0.1-, 0.3%: Trunk/extremities: 61.5%, 71.4%, 70.0% versus vehicle 21.8% Face/neck: 70.6%, 75.0%, 77.8% versus vehicle: 27.3%	AE recorded by unknown personnel and lab tests performed at all study intervals.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Ruzicka, 1997 Europe European Tacrolimus Mutlicenter Atopic Dermatitis Study Group Fair	59.3-62.3% randomized to tacrolimus experienced at least 1 AE compared with 42.6% receiving vehicle. Burning sensation at the site of application was the only even with a significantly higher incidence than vehicle (37% vs. 49% vs. 49% vs. 14.8%). Other AEs at site of application occurring in all arms: pruritus, erythema AE that led to WD at the site of application: 1 patient with foliculitis on 0.03%, 3 patients with burning and 1 patient with pruritus on 0.1%, 2 patients with burning and 1 patient with suspected viral skin infection on 0.3%; vehicle arm: 2 patients with burning and pruritus	Total WD: Tacro 0.03%- 13% Tacro 0.1%- 13% Tacro 0.3%- 14% Vehicle- 39% WD due to AE: Tacro 0.03%- 2% Tacro 0.1%- 7% Tacro 0.3%- 6% Vehicle- 9%	Baseline score 2 was not reported for comparison of the secondary endpoint.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Boguniewicz, 1998 US Fair	Double-blind, multicenter	7 -16 years with 5% to 30% body surface area involvement and moderate-to-severe atopic dermatitis according to the criteria of Hanifin and Rajka. Patients requiring antiinfective drugs were excluded. Nonsedating antihistamines were discontinued before enrollment. Menstruating female patients had to have a negative pregnancy test result and practice effective birth control.	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Boguniewicz, 1998 US Fair	Tacrolimus 0.03-, 0.1-, or 0.3% ointment applied twice daily versus vehicle-alone (ointment based) x 22 days with a 2-week follow-up period	Run-in: NR Washout: stop topical and inhaled corticosteroids x 1 week; systemic steroids x 6 weeks; immunotherapeutic agents and ultraviolet light therapy x 1 month prior to enrollment	Nonmedicated emollients allowed

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Boguniewicz, 1998 US Fair	Physician's Global Evaluation (PGE) of clinical response compared with baseline. Secondary endpoints: mEASI, a Head and Neck Total Score, patient's self-assessment of pruritus and overall treatment effect. Outcomes measured at baseline, day 4, day 8, day 14, day 22, day 29, day 36.	10.1-10.8 (SD 2.2-2.9) Female 47.7-59% White 55.8-77.6% Black 20.4-31.8%	Duration of AD: 3.4-3.7 yrs BSA involved: 7.4-8.6% Severe severity index: 5-12 Moderate severity index: 32-42	NR NR 180

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Boguniewicz, 1998 US Fair	18 NR 169 (93.8%)	For tacrolimus 0.03-, 0.1-, 0.3%: PGE: 69%, 67%, 70% vs. 38% for vehicle (p=0.005, 0.007, 0.004 vs. vehicle) mEASI: 72%, 77%, 81% vs. 26% for vehicle, p<0.001 Head/Neck Total score: 65%, 83%, 81% vs. 2% worsening in vehicle arm, (p<0.001 vs. vehicle) % patients reporting feeling 'much better' or 'better': 76%, 91%, 91% vs. vehicle 52% (p<0.03 for tacrolimus vs. vehicle)	Did not report who assessed AE

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Boguniewicz, 1998 US Fair	Tacro 0.03%-, 0.1%-, 0.3%-, vehicle: ↑Scr: 2.3%, 0%, 0%, 0% (transient ↑ to 1.4 mg/dL which resolved without change in study drug application) ↑pruritus at application site: 25.6%, 20.4%, 29.5%, 15.9% Skin burning at application site: 20.9%, 10.2%, 22.7%, 6.8% ↑erythema at application site: 0%, 2.0%, 6.8%, 4.5%	Total WD: Tacro 0.03%- 4.7% Tacro 0.1%- 10.2% Tacro 0.3%- 9.3% Vehicle- 15.9% WD due to AE: Tacro 0.03%- 0% Tacro 0.1%- 2.0% Tacro 0.3%- 9.1% Vehicle- 4.5%	

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Schachner, 2005 NR Fair	Double-blind, multicenter (18 study sites)	2-15 yrs with a diagnosis of mild or moderate AD involving 2%-30% BSA; diagnosis of AD was made by using Hanifin and Rajika criteria; degree of severity was rated by using the Investigators' Global Atopic Dermatitis Assessment (IGADA) using scores based on the Physician Assessment of Individual Signs. Patients were required to meet the entrance criteria and follow specific prestudy and concomitant therapy restrictions. Patients were excluded if they had a skin disorder other than AD in the area to be treated, clinically infected AD, a known hypersensitivity to macrolides or any of the excipients of the ointment, or previous use of tacrolimus ointment for AD or if they were pregnant or nursing. Nonsteroidal immunosuppressants, other investigational drugs, systemic corticosteroids, UV light therapy (UVA, UVB), as well as concomitant topical medications (including topical corticosteroids, topical H1 and H2 antihistamines, and topical antimicrobials) were not allowed.	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Schachner, 2005 NR Fair	Tacrolimus 0.03% ointment, vehicle ointment; applied twice daily x 6 weeks. If treated areas completely cleared before the 6-week visit, treatment continued in all areas for 1-additional week and was followed to end of study. No treatments continued beyond 6 weeks.	Run in: NR Washout: 4 weeks washout depending on prior therapy	Intranasal or inhaled corticosteroids were permitted if use was restricted to FDA-approved indications and doses did not exceed the maximal approved doses. Use of sunscreen was allowed, and application of nonmedicated emollients was permitted on nontreatment areas. Use of cosmetics on treatment sites was prohibited. Oral antihistamines were allowed only if the patient was on a stable dose at baseline; however, the dosage could be decreased or discontinued (but not increased) during the study.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Schachner, 2005 NR Fair	Treatment success rate defined as the % of patients with IGADA scores designated as "clear" or "almost clear" at 6 weeks. Failure was designated as other IGADA scores.; EASI% of total BSA affected; patient assessment of itch using 10-cm VAS. Measured at baseline, day 4, weeks 2, 4, 6	6.7-7.9 (SD 4.0-4.1) Female 53% White 65-71% Black 23% Asian 4-6% Other 1-5%	>50% were between 2-6 yrs Mild severity AD: 60-61% Moderate severity AD: 39-40% Head/neck involvement: 54-59% Mean % BSA involved: 12.3-12.5 (SD 7.7-9.1) Mean EASI score: 5.9-6.3 (SD 4.5-4.6) Itch score in cm: 4.9	NR NR 317

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Schachner, 2005 NR Fair	90 (28.4%) 24 317	% of patients achieving "treatment success" per IGADA score for tacrolimus vs. vehicle: 50.6% vs. 25.8%, p<0.0001 Stratified by mild disease: IGADA "treatment success" score for tacrolimus vs. vehicle: 56.7% vs. 32.3%, p=0.0007. Stratified by moderate disease for "success" per IGADA for tacrolimus vs. vehicle: 41.0% vs. 15.9%, p0.001 %improvement in EASI score from baseline (for tacrolimus vs. vehicle): 54.8% vs. 20.8%, p<0.0001 Head/neck EASI score (%) for tacrolimus vs. vehicle: 59.1% improved vs. 3.9% worsened, p<0.01 %BSA affected for tacrolimus vs. vehicle: 50.5% reduction vs. 16.4% decrease, p<0.0001 Mean Itch score for tacrolimus vs. vehicle: From 4.9cm to 2.1cm vs. from 4.9cm to 3.7cm, p<0.0001	Patient, caregiver, or investigator

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Schachner, 2005 NR Fair	Overall incidence of AE for tacrolimus vs. vehicle: 36.7% vs. 45.3%, p=0.12 Early withdrawal due to application site reaction: 2.5% vs. 7.5%, p=0.04 The most frequent cutaneous AE observed in both arms was increased itching (tacrolimus vs. vehicle): 23.4% vs. 33.3%, p=0.05 Skin erythema for tacrolimus vs. vehicle: 7.6% vs. 18.9%, p=0.003 Skin burning/stinging for tacrolimus vs. vehicle: 19.0% vs. 17.0%, p=0.64 Folliculitis, skin infection, and acne were reported in a small number of patietns and were comparable between treatment arms (data not reported). None of the patients in either arm experienced warts, molluscum, herpes simplex, or herpes zoster. A single case of eczema herpeticum was reported in a patient treated with vehicle.	90 (18.4% for tacrolimus and 38.4% for vehicle) 19 (6% total; 4.4% for tacrolimus and 7.5% for vehicle)	

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Paller, 2001 US Fair	Double-blind, multicenter (23 centers)	2-15 yrs; moderate to severe atopic dermatitis (based on criteria developed by Hanifin and Rajka and Rajka and Langeland) involving 10% to 100% of body surface area Exclusion: other serious skin disorder, pigmentation, or extensive scarring in affected areas; clinically infected atopic dermatitis; any systemic disease that would contraindicate the use of tacrolimus; any chronic condition that was not well controlled; pregnancy or lactation	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Paller, 2001 US Fair	Tacrolimus 0.03-, 0.1% ointment, vehicle ointment; applied twice daily x 12 weeks Individual cleared lesions could be excluded from treatment after the week 3 evaluation, provided the newly cleared area had been treated for 1 week after clearing. Treatment was ended at week 12 whether or not a complete clearance in all baseline treatment areas had been achieved.	Run in: NR Washout: 1 day to 6 weeks depending on prior intervention	Use of sedating antihistamines such as diphenhydramine was permitted during the study if patient was receiving a stable dose at baseline; the dosage could be decreased or discontinued, but not increased during the study; nonmedicated emollients to unaffected areas only

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Paller, 2001 US Fair	Primary endpoint: treatment success per Physician's Global Assessment (defined as cleared or excellent improvement ≥90% improvement). Secondary endpoint: % BSA affected, total score, EASI, patient self-assessment and pruritus assessment Baseline, weeks 1, 2, 3, 6, 9, 12	2-6 yrs: 58.5-63.2% 7-15 yrs: 36.8-41.5% Female 51.7-54.3% White 63.6-67.2% Black 24.1-28.8% Asian 5.1-6.9% Other 1.7-2.5%	Moderate severity: 36.4-4.05% Severe severity: 59.5-63.6% Head/neck involvement: 78.8-86.2% % BSA affected 45.6-49.2%	NR NR 351

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Paller, 2001 US Fair	105 NR 351	% achieving treatment success for tacrolimus 0.03-0.1%, and vehicle: 35.9% vs. 40.7% vs. 6.9%; p= NSD for the different tacrolimus dosages; p<0.001 vs. vehicle Similar significant treatment group differences were observed for the patient's assessment of overall response ; more tacrolimus-treated patients reported better or much better response than those treated with vehicle, p<0.001 (data not shown). Reduction in pruritus score for tacrolimus 0.03-, 0.1, and vehicle: -3.9 vs. -3.9 vs. -0.9 (estimated from graph), p<0.001 vs. vehicle Reduction in % BSA affected: 26% vs. 27% vs. 7% (estimated from graph), p<0.001 vs. vehicle Reduction in EASI: -14 vs. -15.1 vs. -2.1 (estimated from graph), p<0.001 vs. vehicle Reduction in total score for signs of AD: -5.9 vs. -6 vs. -1.5 (estimated from graph), p<0.001 vs. vehicle	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Paller, 2001 US Fair	Data not shown for nonapplication site adverse events. Rate of individual adverse events for tacrolimus 0.03-, 0.1%, and vehicle: Skin burning: 42.7% vs. 33.7% vs. 29.0% Pruritus: 41.2% vs. 32.2% vs. 26.6% Varicella: 4.8% vs. 1.1% vs. 0.0% Vesiculobllous rash: 3.8% vs. 1.0% vs. 0.0% Sinusitis: 3.3% vs. 1.0% vs. 8.0% p<0.05 for tacrolimus 0.03% vs. vehicle for skin burning, pruritus, varicella, vesiculbollous rash, sinusitus p= NSD for tacrolimus 0.1% vs. vehicle for all the above except for p<0.05 for sinusitus	105 18 (5.1%)	Unclear whether data for AE were selectively reported.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Hanifin, 2001 US Fair	Double-blind, multicenter This pooled study includes data from 2 larger unpublished trials. Both trials were of identical study design. These 2 trials were later identified in the FDA dossier as study #35 and #36.	Adult patients with a diagnosis of atopic dermatitis (based on Hanifin and Rajka criteria) involving 10% to 100% of BSA, were enrolled in the study. Patients were required to meet the entrance criteria, including severity of at least moderate (4-5) by Rajka and Langeland scoring, and to follow specific prestudy and concomitant therapy restrictions Excluded: Other serious skin disorder, pigmentation, or extensive scarring in affected areas; clinically infected atopic dermatitis; any systemic disease that would contraindicate the use of tacrolimus ointment; any chronic condition that was not well controlled; pregnancy or lactation Excluded medications: astemizole; terfenadine; other nonsedating antihistamines; other investigational drugs, nonsteroidal immunosuppressants; light treatments (UVA, UVB); systemic corticosteroids Intranasal and/or inhaled corticosteroids; if >2 mg prednisone equivalent required per day; Topical corticosteroids, topical H1 and H2 antihistamines, topical antimicrobials; other medicated topical agents; nonmedicated topical agents (including 1 day creams, lotions, and emollier	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Hanifin, 2001 US Fair	Tacrolimus 0.03-, 0.1%, vehicle ointment; applied twice daily x 12 weeks	Run-in: NR Washout: 1 day to 6 weeks depending on prior treatment	The use of sedating antihistamines such as diphenhydramine was permitted during the study if patient was on a stable dose at baseline; the dosage could be decreased or discontinued, but not increased during the study.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Hanifin, 2001 US Fair	Physician Global Evaluation of clinical response at 12 weeks (defined as clear or excellent 90-100%), physician's assessment of clinical signs of AD, EASI score, % change in affected BSA, patient self-assessment of pruritus using 10-cm VAS. Baseline, weeks 1, 2, 3, 6, 9, 12	Pooled results: 37.9-39.3 yrs (13.8-14.5) Female 55.2-59.3% White 66.0-68.2% Black 24.5-26.4% Other 5.6-9.1%	Pooled results % with Moderate severity: 41.1-46.2% % with Severe severity: 53.8-58.9% % Head/Neck involvement: 85.6-89.2% % BSA affected: 44.9-45.5% (SD25.7-27.0)	NR NR 632

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Hanifin, 2001 US Fair	258 NR 632	% achieving success rate (defined by 90-100% improvement in physician global evaluation) for tacrolimus 0.03-, 0.1%, and vehicle: 27.5% vs. 36.8% vs. 6.6% (p<0.001 vs. vehicle) Data for EASI, BSA, pruritus score were estimated from bar graphs. Actual results were not presented for the pooled arms. Mean change in EASI score from baseline: -11.9 vs. -15 vs. -2.1, p<0.001 vs. vehicle and p=0.001 for 0.03% vs. 0.1% Mean change in % BSA affected from baseline: -18 vs. -24 vs. -5, p<0.001 vs. vehicle and p=0.001 for 0.03% vs. 0.1% Mean change in pruritus score from baseline: -3.4 vs. -3.5 vs. -0.7, p<0.001 vs. vehicle	NR in this publication

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Hanifin, 2001 US Fair	NR in this publication	Did not abstract these results	Results for AE were published in another publication by Soter, 2001 Results for EASI, BSA, and pruritus scores were not provided in this publication--actual results were available in the FDA review and are reported in this evidence table

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Study 1 (#35 in FDA review)--published in Hanifin, 2001	see above	see above	see above
Study 2 (#36 in FDA review)--published in Hanifin, 2001	see above	see above	see above

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Study 1 (#35 in FDA review)--published in Hanifin, 2001	see above	see above	see above
Study 2 (#36 in FDA review)--published in Hanifin, 2001	see above	see above	see above

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Study 1 (#35 in FDA review)--published in Hanifin, 2001	see above	38.0-39.3 yrs (SD13.0-13.8) Female 51.0-61.6% White 65.7-67.0% Black 26.3-29.4% Other 4.9-7.1%	% with Moderate severity: 39.4-52.4% % with Severe severity: 47.6-60.6% % Head/Neck involvement: 79.6-89.2% % BSA affected: 41.4-43.4% (SD 24.5-26.7)	NR NR 304
Study 2 (#36 in FDA review)--published in Hanifin, 2001	see above	37.9-39.2 yrs (SD 13.8-15.8) Female 50.0-59.1% White 66.4-69.4% Black 24.5-26.4% Other 5.6-9.1%	% with Moderate severity: 36.1-44.5% % with Severe severity: 55.5-63.9% % Head/Neck involvement: 89.1-92.6% % BSA affected: 47.2-48.2% (SD 26.7-28.0)	NR NR 328

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Study 1 (#35 in FDA review)--published in Hanifin, 2001	122 NR 304	% achieving success rate (90-100% improvement in PGE): 29.1% vs. 35.4% vs. 7.8%, p<0.001 vs. vehicle Actual data for EASI, BSA, pruritus score are from the FDA review since only bar graphs were provided for these outcomes in this publication. Mean change in EASI score from baseline: -12.6 vs. -13.8 vs. -3.4 (p<0.001 vs. vehicle) Mean change from baseline in % BSA affected: -19.9% vs. -22.0% vs. -6.9% (p<0.001 vs. vehicle) Mean change from baseline in pruritus score: -3.8 vs. -3.6 vs. -0.7 (p<0.001 vs. vehicle)	NR in this publication
Study 2 (#36 in FDA review)--published in Hanifin, 2001	136 NR 328	% achieving success rate (90-100% improvement in PGE): 25.9% vs. 38.2% vs. 5.5%, p<0.001 vs. vehicle Actual data for EASI, BSA, pruritus score are from the FDA review since only bar graphs were provided for these outcomes in this publication. Mean change in EASI score from baseline: -10.7 vs. -15.9 vs. -1.6 (p<0.001 vs. vehicle) Mean change from baseline in % BSA affected: -17.9% vs. -27.0% vs. -3.2% (p<0.001 vs. vehicle) Mean change from baseline in pruritus score: -3.1 vs. -3.5 vs. -0.6 (p<0.001 vs. vehicle)	NR in this publication

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Study 1 (#35 in FDA review)--published in Hanifin, 2001	NR in this publication	122 24	study #35 age range was 15 77 yrs (from FDA review)
Study 2 (#36 in FDA review)--published in Hanifin, 2001	NR in this publication	136 26	study #36 age range was 16 79 yrs (from FDA review)

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Soter, 2001 US Fair	companion to Hanifin, 2001 (above)	see above	see above

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Soter, 2001 US Fair	see above	see above	see above

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Soter, 2001 US Fair	see above	see above	see above	see above

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Soter, 2001 US Fair	see above	see above	NR; safety was assessed by the incidence of events and changes from baseline in lab values

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Soter, 2001 US Fair	Pooled data was provided in this publication. Results are reported for vehicle, tacro 0.03- and 0.1% Skin burning 25.8% vs. 45.6% vs. 57.7% Pruritus 36.5% vs. 46.1% vs. 46.1% Skin erythema 19.8% vs. 24.8% vs. 27.9% Skin infection 10.6% vs. 12.4% vs. 4.7% Acne 1.8% vs. 4.3% vs. 7.1% Alcohol intolerance 0.0% vs. 3.4% vs. 6.9% Hyperesthesia 0.5% vs. 3.0% vs. 6.5% # of cases of viral adverse events: Herpes simplex 4 vs. 9 vs. 7 Eczema herpeticum 0 vs. 2 vs. 1 Molluscum contagiosum 0 vs. 1 vs. 1 Herpes zoster 0 vs. 1 vs. 1 Leukopenia 1 vs. 0 vs. 1 (these cases were deemed unlikely study drug related)	see above	

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (other atopic-related ailments)?
Chapman, 2005 US *Note: did not include efficacy data in analysis but used for safety information	Double-blind, multicenter This pooled study includes data from 2 larger trials (1 of which is Schachner). Both trials were of identical study design.	Mild to moderate AD that covered 2% to 30% of their total body surface area (BSA). Patients in the pediatric study were age 2 to 15 years and those in the adult study were age 16 years and older. Patients were excluded if they had skin disease other than AD in the treatment area such as infections and dyspigmentation, had previously used tacrolimus ointment for AD, or had a known hypersensitivity to macrolides or excipients of the ointment. The following treatments were prohibited during the study: nonsteroidal immunosuppressants, UV light therapy (UVA, UVB), systemic and topical corticosteroids, topical antihistamines, topical antimicrobials, and any other medicated topical agent.	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Chapman, 2005 US *Note: did not include efficacy data in analysis but used for safety information	Tacrolimus 0.03% ointment vs. vehicle; applied twice daily x 6 weeks	Run-in: NR Washout: up to 4 weeks	Nonmedicated topical agents were permitted only in the areas not being treated with study medication. Intranasal or inhaled corticosteroids were permitted if use was restricted to 2 mg/d or less (prednisone equivalent). Systemic antihistamines were permitted only if the patient was taking a stable dose at baseline; this dose could be decreased or discontinued (but not increased) during the study. Sunscreens were permitted throughout the study; use of cosmetics on treatment sites was prohibited.

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Race/Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Chapman, 2005 US *Note: did not include efficacy data in analysis but used for safety information	Primary endpoint: % of patients designated as treatment success by IGADA method Secondary: EASI score, % BSA affected, patient assessment of pruritus	For the pooled analysis: 15 yrs Female 58.6-59% White 69.7-70.4% Black 21.6-23.8% Other 5.9-8.7% Children study; mean age range 5.5-6 yrs Adult study; mean age range 37.5-38.5 yrs	For pooled analysis: % of patients with IGADA Mild severity: 61-62.5% % with IGADA Moderate severity: 37.5-39% Head/neck involvement: 50.5-51.6% Mean EASI score: 5.5 % BSA affected: 11.0-11.2% Itch score: 4.9cm	NR NR 618

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Results (frequency of rebound flares, reduction in sx severity, time to next flare up (treatment duration), QL, treatment failure (use of other agents)	Method of adverse effects assessment
Chapman, 2005 US *Note: did not include efficacy data in analysis but used for safety information	152 39 617	For pooled analysis: % with treatment success per IGADA for tacrolimus and vehicle: 49.7% vs. 29%, p<0.001 % improvement in EASI score: 55.4% vs. 25.4%, p<0.001 % improvement in affected BSA: 47.2% vs. 21.6%, p<0.001 Change in itch score from baseline: -2.5 vs. -1.2, p<0.001 % improvement in EASI score for Head/neck: 52.3% vs. 8.6%, p=0.005 For children study arm: % with treatment success per IGADA: 50.6% vs. 25.8%, p<0.001 For adult study arm: % with treatment success per IGADA: 48.7% vs. 32.4%, p=0.004	NR

Evidence Table 7. Placebo-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Chapman, 2005 US *Note: did not include efficacy data in analysis but used for safety information	For pooled analysis: Skin burning/stinging 27.4% vs. 24.8% Itching: 29% vs. 37.5% Skin erythema 12.9% vs. 24.1% Skin infection 1.9% vs. 2.3% Folliculitis 1.9% vs. 3.3% Acne 2.3% vs. 1.6% Herpes simplex 0.6% vs. 0.3% Eczema herpeticum 0.0% vs. 0.3% No cases of molluscum contagiosum or herpes zoster	152 32	Did not meet planned sample size of 640 for the pooled analysis. The authors of this analysis did not provide individual trial results for all outcomes (only provided for IGADA assessment).

Evidence Table 8. Quality assessment of placebo-controlled trials of tacrolimus

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Ruzicka, 1997 Europe	Method not described	Method not described	Patients in 0.03% arm had larger trunk/extremity involvement by ~300 cm^2 than other arms	Yes	Yes	Yes	Yes
Boguniewicz, 1998 US	Yes, centralized computer-generated randomization schedule	Yes	Patients randomized to vehicle had higher severity index score of 12 compared with other tacrolimus arms of scores 5-7. There was some difference in the % of BSA involved between tacrolimus 0.1% arm and the rest of the treatment arms	Yes	Yes	Yes	Yes
Schachner, 2005 NR	Yes, centralized computer-generated randomization schedule	Yes	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Paller, 2001	Method not described	Method not described	Yes	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials of tacrolimus

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Ruzicka, 1997 Europe	Yes NR NR NR	Yes (13-14% tacrolimus versus 39% vehicle)/ No (19.7% total)	Yes, LOCF	No	Fair	Fujisawa
Boguniewicz, 1998 US	Yes NR Yes NR	Yes, differential (4.7-10.2 tacrolimus versus 15.9% vehicle)/ No (10% total)	Borderline (~94% analyzed), unclear how missing data were handled Note: primary analysis for efficacy involved data from all patients receiving at least 3 consecutive days of study drug (93.8% were analyzed)	No	Fair	Fujisawa USA
Schachner, 2005 NR	Yes NR NR NR	Yes, differential (18.4% tacrolimus vs. 38.4% vehicle) Yes (28.4% total)	Yes, LOCF	No	Fair	Astellas
Paller, 2001	Yes NR NR NR	Yes, differential 14.4%-19.7% tacrolimus vs. 56.0% vehicle) Yes (29.9% total)	Yes, unclear how missing data were handled	No	Fair	Fujisawa

Evidence Table 8. Quality assessment of placebo-controlled trials of tacrolimus

	Internal Validity						
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Hanifin, 2001 US	Method not described	Method not described	No, ~10% difference in baseline moderate severity between vehicle and tacro 0.1% arms in study 1; ~10-13% more patients had severe disease in the tacro 0.1% arm compared to the other arms	Yes	Unclear, reported as double blind	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 8. Quality assessment of placebo-controlled trials of tacrolimus

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Hanifin, 2001 US	Yes NR NR NR	Yes (40.8%)/Yes	Yes but unclear how missing data were handled	No	Fair	Fujisawa

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (asthma, other atopic-related ailments, infections)?
Luger, 2004 Europe Fair	Double-blind, multicenter (35 centers in 9 countries)	18-79 years with atopic dermatitis diagnosed according to Williams criteria; with moderate-severe disease affecting ≥5% of total BSA. Exclusion: treatment with phototherapy; radiation therapy or systemic therapy for atopic dermatitis in the previous month; treatment with topical therapy (other than tar shampoo on the scalp) not stopped 24 hr before 1st application of study medication; malignancy or immunosuppression; known HIV-positive status; acute or chronic bacterial, viral or fungal diseases; active skin infections (ie, herpes simplex infections); and presence of skin conditions that could affect the evaluation of study treatment (ie, generalized erythoderma such as Netherton's syndrome and psoriasis)	NR (see exclusion criteria)

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Luger, 2004 Europe Fair	Pimecrolimus 1% cream versus Triamcinolone acetonide cream 0.1% (trunk and limbs) and Hydrocortisone acetate cream 1% (face and neck). Applied twice daily x 12 mos. There was no limitation on the amount and duration of drug usage over 12 mos.	NR/NR	Antihistamines and emollients only	Primary endpoint: Safety and tolerability: Patients were to record AE on diary cards every day. Incidence of bacterial, viral, or fungal infections of the skin were prospectively assessed (unclear by whom and by which method-active or passive). Application site reactions were also recorded. Labs and PE were performed. Secondary endpoint: Efficacy: EASI score, Investigator Assessment (IA), time to 1st recurrence, time to 1st remission. Patients were assessed at baseline, days 8, 22, 43, and then monthly until end of study period. An additional visit was performed post-treatment--the day after the last application of study med).

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Age (yrs) Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Luger, 2004 Europe Fair	33.4-33.5 Female 53.6-55.5 White 88.8-89.6% Black 1.8-4.5% Asian 3.0-4.9% Other 2.1% Missing 1.5%	mean %BSA involved: 26.5-27.0 (SD19.26) % Head/neck involved: 89.6-89.7 mean EASI: 15.0-15.3 (SD10.9-10.95) % with disease severity: Mild (score 3-4): 2.1-3.0 Moderate (score 4.5-7.5): 63.6-65.9 Severe (score 8-9): 32-33.3 Mean height: 170.2 cm Mean weight: 69.6-69.8 kg	NR NR 658	Total number withdrawn- NR NR 658 for harms

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Luger, 2004 Europe Fair	Mean % of days on which patients needed to apply study med for pimecrolimus and triamcinolone: 88.7% vs. 83.4% Median % of days of exposure to study med for pimecrolimus and triamcinolone: 99.5% vs.95.6% For between-group comparisn, median EASI scores were lower with triamcoinolone than pimecrolimus at all time points, p<0.006 from baseline to study end (data reported in graph format only). No significant differences between triamcinolone or pimecrolimus at end of study for Investigator Assessment score of 0-3: 88.8% triamcinolone vs. 81.5% pimecrolimus, p=0.067.	Patient report and investigator assessment

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Luger, 2004 Europe Fair	For the most frequently reported skin infections (Table II), there were no statistical differences in these AE between pimecrolimus and triamcinolone except for he incidence of viral skin papilloma (treatment difference 2.1%, 95% CI -3.7, -0.6), which occurred more frequently with triamcinolone (2.1%) than pimecrolimus (0%). However, overall, none of the treatment differences exceeded 5%. For those with >30% BSA involvement, the overall incidence of bacterial skin infections was higher with triamcinolone (19.8%) than pimecrolimus (9.6%), which was statistically significant (95% CI -19.5, -0.9). More triamcinolone-treated subjects (12.6%) reported bacterial folliculitis than pimecrolimus (4.8%) leading to statistical significant difference (treatment difference -7.8%, 95% CI -15.2, -0.4). 3 patients (0.9%) on triamcinolone reported skin striae compared with 0% pimecrolimus. 3 pimecrolimus-treated subjects reported serious skin and tissue disorders: exacerbation of AD, contact dermatitis, and infected eczema. Application site reactions were reported more frequently wit Total 46.3% vs. 24.2% (most common was burning)	NR Total number of withdrawals due to AE-NR, however, withdrawal due to "application site reaction" were reported (7.6% for pimecrolimus vs. 0.9% triamcinolone)	To maintain blinding, both topical steroid and pimecrolimus could be used without limitation for the total daily dose applied and for the duration of treatment.

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidity (asthma, other atopic-related ailments, infections)?
Luger, 2001 Europe Fair	Double-blind, multicenter (14 centers in 7 countries)	≥18 yrs with atopic dermatitis diagnosed according to Hanifin and Rajka criteria; severity of the patients' atopic dermatitis was evaluated according to the grading system of Rajka and Langeland and had to be of at least moderate severity at baseline. The disease affected between 5% and 30% of the total body surface area. The use of other treatments for atopic dermatitis (including emollient use at treated sites), or corticosteroids (inhaled or oral) for the treatment of asthma during the treatment phase of the study was prohibited. Patients with concomitant medical conditions that could interfere with the evaluation of the study were excluded, as were women who were pregnant, breast feeding, or not using medically approved contraception if they were of child-bearing potential.	NR (see exclusion criteria)

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Interventions	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Luger, 2001 Europe Fair	Pimecrolimus 1% cream, betamethasone-17-valerate 0.1% cream, vehicle; applied twice daily (except to face) x 3 weeks	NR/NR	NR	Used adapted EASI scoring system (omitted scores for the head area which accounts for 10% of the total BSA). Patients assessed pruritis using scoring system ranging from 0-3 (assessed the intensity of itch in the previous 24 hr). Patients assessed overall improvement of atopic dermatitis using a score ranging from 0-6.

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Age (yrs) Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Luger, 2001 Europe Fair	28-33 Female 46.7-54.8% White 95.3-100%	Median duration of disease: 22-25 yrs mean EASI score: 10.12-11.28 >90% have moderate severity atopic dermatitis in all treatment arms	NR NR 260 (130 for vehicle, pimecrolimus 1%, and betamethasone arms)	29 2 130 *data reported only for 3 arms

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Luger, 2001 Europe Fair	Median EASI scores for vehicle, pimecrolimus 1%, and betamethasone-17-valerate 0.1%: Change from baseline: 0% vs. 45%, vs. 80% (p=0.008 for vehicle vs. pimecrolimus, p-value= NR for betamethsone vs. pimecrolimus) Patient assessment in Pruritus score (improvement) for vehicle vs. pimecrolimus, and betamethasone: Change from baseline: 18.6% vs. 46.7% vs. 81% Patient assessment of atopic dermatitis improvement for vehicle, pimecrolimus, and betamethasone: Change from baseline: 16.3% vs. 53.3% vs. 88.1% EASI data were also stratified by disease severity which showed that with increasing severity, there was a decline in treatment effect (see Table 4)	Labs, PE, VS were collected; unclear who assessed adverse events

Evidence Table 9. Active-controlled trials of pimecrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Luger, 2001 Europe Fair	Application site reactions were the most commonly reported AE. For vehicle, pimecrolimus 1%, and betamethasone, the rates were: 35% vs. 49% vs. 10%. Most application site reactions began on the 1st day of treatment and resolved within the 1st 3 days of therapy. Rates of pruritus for vehicle, pimecrolimus, betamethasone: 35% vs. 31% vs. 12% Rates of worsening disease for vehicle, pimecrolimus, betamethasone: 21% vs. 4% vs. 2%	29 11	Per the Rajka and Langeland criteria for assessing baseline severity: A score >4 or <8 is moderate. A score 8-9 is severe.

Evidence Table 10. Quality assessment of active-controlled trials of pimecrolimus

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Luger, 2004	Method not described	Method not described	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind
Luger, 2001	Method not described	Method not described	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind

Evidence Table 10. Quality assessment of active-controlled trials of pimecrolimus

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Total withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Luger, 2004	Yes, each patient received 3 tubes of cream with labels for appropriate areas.	Yes NR NR NR	NR NR-Total withdrawal rate not reported for both arms, 58.8% withdrew from pimecrolimus arm. Of the 30% with severe disease, 36.3% pimecrolimus vs. 8.2% topical steroid withdrew due to unsatisfactory therapeutic effect.	Yes, for safety. No, for efficacy: used observed data.	No	Fair
Luger, 2001	Unclear, reported as double-blind	Yes NR NR NR	29 Yes, there was high differential seen with those randomized to vehicle compared with the other arms	Yes; unclear how missing data were handled	No	Fair

Evidence Table 10. Quality assessment of active-controlled trials of pimecrolimus

Author, Year Country	Funding
Luger, 2004	Novartis
Luger, 2001	NR

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Bieber, 2007 Germany, Italy, Spain Fair	Double-blind, multicenter (25 centers)	2-15 yrs experiencing an acute severe of very severe flare of atopic dermatitis (defined by IGA score ≥4); history of moderate to severe atopic dermatitis for at least 1 yr; minimum affected BSA 5%; avoidance of excessive exosre to natural or artificial sunlight;. Exclusion: previous systemic therapy for atopic dermatitis or phototherapy (< 4 weeks); vaccination (< 4weeks); antihistamine treatment (<2 weeks); local therapy with tacrolimus, pimecrolimus or glucosteroids (<1 week); pregnancy or breast feeding; indication for systemic therapy; hypersensitivity to study medications or macrolides; lymphadenopathy; immune deficiency; hepatic or renal insufficiency; acute herpes simplex, mononucleosis or mollusca contagiosa infection; acute and severe impetigo contagiosa; severe other viral, bacterial, or fungal skin infections; acute infestations; generalized erythroderma; Netherton's syndrome	NR (see exclusion criteria)	Tacrolimus 0.03% ointment twice daily versus Methylprednisolone aceponate (MPA) 0.1% once daily (vehicle ointment administered to maintain blinding) x 3 weeks

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Bieber, 2007 Germany, Italy, Spain Fair	NR/NR	Nonmedicated emollients and bath oil	Primary endpoint: static IGA score Secondary endpoint: EASI, the affected BSA, patient's assessment of itch and sleep using 100 mm VAS, modified EASI, Children's Derm Life Quality Index (CDLQI), patient's assessment of the change of the disease Study evaluations performed at baseline days 4 and 7, weeks 2 and 3.	7.5-7.8 yrs (SD 4.2) NR White 94.5-98.5% Black 0.7-2.3% Asian 0.7-2.3%

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bieber, 2007	43-47% between 2-6 years	266	8
Germany, Italy, Spain	27.9-31% between 7-11 years	265	2
Fair		265	265
	EASI 18.7 Itch 63.6-68.0 mm VAS Sleep 51.5-54.6 mm VAS % affected BSA 28.8-29.4%		

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Bieber, 2007 Germany, Italy, Spain Fair	IGA score 'clear' or 'almost clear' for tacrolimus and MPA: 66.9% vs. 66.6% (absolute difference 0.3%); p=0.93 at 3 weeks. There was no difference for those achieving 'clear' between the treatment arms (tacrolimus 29.4% vs. MPA 37.2%) at 3 weeks. No difference in mean EASI score at week 3 between treatment arms (estimated from graph tacrolimus 85% vs. MPA 90%), p=0.067. No difference in the %'age of affected BSA from baseline to week 3 between treatment arms (tacrolimus 7.7% vs. MPA 6.8%), p-value= NR. *There was improvement in patient' assessment of itch and quality of sleep for both treatment arms, howevere, there was greater (statistically siginificant improvement) with MPA arm than tacrolimus at 3 weeks, p=0.0004 and p=0.009. mEASI scores similar to EASI scores (data were not reported). CDLQI scores on 'symptoms and feelings' and 'sleep' were signficantly larger with MPA than tacrolimus (data not reported). 2 tacrolimus-treated patients reported worsening of disease compared with 0 MPA-treated patients.	Assessment of AE included physical exams; did not report who assessed AE

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Bieber, 2007 Germany, Italy, Spain Fair	No patients on MPA experienced AE attributed to treatment compared with 4.4% (6 patients) receiving tacrolimus who reported pruritus, erythema, skin burning, and hot flushes. 4 patients in tacrolimus arm discontinued the study due to AE which were deemed drug-related; 1 patient on MPA had medication reduced due to varicella which was not deemed drug-related by investigators.	8 (3.0%) 4	All investigators were trained in the use of IGA scoring system and were provided wih reference photographs

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Torok, 2003 NR Poor	Investigator-blinded Setting: NR	16-65 yrs with history of atopic dermatitis for at least 6 mos affecting between 5-20% BSA (excluding face) and baseline dermatologic sum score (DSS) of at least 5 for the target area (pprox 30-50 cm2). Patients were not eligible if they had underlying disease or other derm conditions that required systemic therapy or use of a topical agent. Patients were not permitted to treat face, scalp, or groin area	NR	Clocortolone pivalate 0.1% cream + tacrolimus 0.1% cream; clocortolone pivalate 0.1% cream alone; tacrolimus 0.1% cream alone; applied twice daily x 21 days
Hung, 2007 Taiwan Poor	Open-label, Setting: single center, outpatient (Dept of Dermatology)	9 mo- 33 yrs with diagnosis of atopic dermatitis according to Hanifin and Rajka criteria; no systemic or topical antibiotics and no systemic or topical corticosteroid use within 4 weeks of study; no clinical sighs of overt secondary infection that needed oral antibiotic therapy; moderate to severe atopic dermatitis at the time of entry according to the Rajka and Langeland criteria.	NR (see exclusion criteria)	Fluticasone propionate 0.05% cream ± fusidic acid 2% cream; tacrolimus 0.03% ointment ± fusidic acid 2% cream; applied twice daily x 8 weeks

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Torok, 2003 NR Poor	NR/NR	Cetaphil Mild Cleanser and Cetaphil Moisturizing Lotion	Used quantitative scales (not specified in the methods section). Physicians evaluated: excoriation, oozing/crusting, induration, lichenification, dryness/scaling, erythema, transient pruritus and burning/stinging; Global assessment (method not reported); dermatologic sum score (DSS); target treatment area Patients evaluated: pruritus and burning/stinging and overall improvement (method not reported); also completed questionnaire on products attributes Baseline, days 3, 7, 14, 21	Mean age: NR 88% < 50 yrs Female 61.4% White 94.7% Black 3.5% Other 1.8%
Hung, 2007 Taiwan Poor	NR/NR	Cetirizine (oral antihistamine); nonmedicated moisturizers	*bacteriological protocol data were not abstracted SCORAD score assessed by 2 clinicans and modified local SCORAD score baseline, week 2, week 8	15.6 yrs Female 56.7% NR (all Taiwanese?)

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Torok, 2003 NR Poor	Skin phototypes I- 19.3% II- 50.9% III- 24.6% IV- 1.8% V- 3.5%	NR NR 57	NR NR 57
Hung, 2007 Taiwan Poor	Mean overall SCORAD 50.0-59.9 (SE 3.2-4.3) mSCORAD 10.6-11.0 (0.6-0.9)	NR NR 60	6 NR NR (60?)

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Torok, 2003 NR Poor	*results for individual treatmen arms reported (combination therapy was not abstracted) Dermatologic sum score for clocortolone and tacrolimus: % mean change from baseline at day 21: -69 (SD 32) vs. -57 (SD 31), p<0.001 vs. baseline for each arm Global severity for clocortolone and tacrolimus: % mean reduction from baseline at day 21: -48 (SD37) vs. -44 (SD 31), p-value= NR Global Improvement for clocortolone and tacrolimus: % improvement at day 21: 57% vs. 26%, p-value= NR	Investigator assessed erythema using a scoring method. Patients scored transient pruritus and burning/stinging.
Hung, 2007 Taiwan Poor	No significant difference was found in BSA involved by atopic dermatitis between fluticasone- and tacrolimus-treated patients (from graph 10% BSA vs. 18% BSA); p= 0.07. Tacrolimus-treated patients had higher subjective scores of pruritus and sleep loss than fluticasone-treated patients, but no significant difference was found at end of study (from graph score of 4 vs. score of 6), p=0.09. No siginificant difference in clinical severity SCORAD score between fluticasone and tacrolimus. Both arms had significant lowering in their clinical severity scores from baseline to week 8; p <0.05.	NR

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Torok, 2003 NR Poor	Transient pruritus and burning/stinging for clocortolone and tacrolimus: Score of 0 to 0.5 vs. score of 0 to 0.5, p-value= NSD Erythema scores for clocortolone and tacrolimus: Change in score from baseline: 1.26 vs. 1.24	NR NR	Skin phototype-classification system based on a person's sensitivity to sunlight; People with type I and II are at the highest risk for photoaging (includes wrinkles and cancer). Fitzpatrick system. Dermatologic sum score: the sum of scores for excoriation, induration, and erythema.
Hung, 2007 Taiwan Poor	NR for individual fluticasone and tacrolimus arms. 2 patients receiving a combination of tacrolimus+fusidic acid withdrew due to intolerance to burning sensation.	6 2 (combination arm)	SCORAD index range 0-103; modified SCORAD assesses 6 items: 1) erythema/darkening; 2) edema/papulation; 3) oozing/crusting; 4) excoriation; 5) lichenification/prurigo; 6) local dryness. Each item was graded ona 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe). Scores ranged from 0-18.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Reitamo, 2002 (C) 6 European countries, Canada Fair	Double-blind, multicenter (27 centers)	2 - 15 yrs with diagnosis of AD according to Hanifin and Rajka. Patients required to have AD severity grading of moderate to severe according to Rajka and Langeland and have disease involvement between 5%-60% BSA. Exclusion: Serious skin disorder other than AD that required treatment; patients with history of eczema herpeticum. Patients were not allowed: topical and systemic corticosteroids, antimicrobials and antihistamines, coal tar, topical nonsteroidal anti-inflammatory drugs, nonsteroidal immunosuppressants, UV light treatments (UVA and UVB), hypnotics and sedatives, and other investigational drugs.	NR	Tacrolimus 0.03-, 0.1%, and Hydrocortisone acetate 1%; all were ointments applied twice daily x 3 weeks. Treatment to stop 7 days after leisons have cleared.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Reitamo, 2002 (C) 6 European countries, Canada Fair	Run-in: NR Washout: for prior treatments ranged from 5 days-6 weeks	Inhaled or intranasal corticosteroids were limited to 1 mg/d. Bath oil and nonmedicated emollients were allowed.	EASI, modified EASI, patient assessment of pruritus using 10-cm VAS, investigator's assessment of overall clinical improvement. Primary endpoint: mEASI mean AUC as a % of baseline. Baseline, days 3, 7, and weeks 2, 3 (and 2 weeks after completion of therapy; week 5)	7.2-7.6 yrs (SD 3.9-4.4) Females: 48.4% - 59.8% White 74.1% - 81.1%

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Reitamo, 2002 (C)	Median duration of current episode: 6.2-10.9 mo Moderate AD: 51.4-60.8% Severe AD: 39.2% - 48.6% Median affected BSA: 23.3 - 26% Affected by body region: Head/neck: 86.5% - 88.2% Upper limbs: 98.9% Trunk: 75.7% - 83.8% Lower limbs: 95.1% - 97.3%	NR NR 560	54 NR 556 (99.3%)
6 European countries, Canada			
Fair			

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Reitamo, 2002 (C) 6 European countries, Canada Fair	Change in mEASI from baseline (mdeian % improvement) for tacro 0.03-, 0.1-, and hydrocort acetate 1% oint: 55.2% vs. 60.2% vs. 36.0% (p<0.001 for tacrolimus doses vs. hydrocortisone) For the Head/Neck, the median mEASI: 62.5% vs. 75.2% 43.3%. Findings for those stratified by younger and older children were no different (data not reported). Median % decrease in BSA (estimated from graph, data not reported): 61% vs. 79% vs 30% Physician's global evaluation of clinical response of excellent/cleared for tacro 0.03-, 0.1-, and hydrocort 1% oint: 38.5% vs. 48.4% vs. 15.7%; Tacro 0.03-and 0.1% vs. hydrocort acetate, p=0.001; Tacro 0.03- vs. 0.1%, p=0.055 (NSD). Findings for EASI and pruritus were similar to those for mEASI and affected BSA (data not shown).	Investigator

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Reitamo, 2002 (C) 6 European countries, Canada Fair	Most common AE at the application site for tacrolimus 0.03-, 0.1, and hydrocortisone acetate: Skin burning: 18.5% vs. 20.4% vs. 7.0% (p<0.05 for tacro arms vs. hydrocortisone) Pruritus: 13.2% vs.11.3% vs. 7.6% Folliculitis 5.8% vs 4.3% vs. 2.7% Skin infection: 3.2% vs. 2.2% vs. 2.2% Skin erythema: 2.1% vs. 0.5% vs. 1.6% AE not at application site: Flu syndrome: 7.9% vs. 7.5% vs. 8.6% Fever: 4.8% vs. 0.5% vs. 4.3% Rhinitis: 0% vs. 3.2% vs. 2.2% Pharyngitis: 1.1% vs. 0.5% vs. 3.2% Diarrhea: 0% vs. 2.7% vs. 1.1%	54 (9.6%) 10 (1.8%)	For those who were evaluated at week 5: In all 3 arms, only half of the patients maintained a moderate improvement in 2 weeks without treatment; these patients observed a worse condition than observed at week 3.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Reitamo, 2002 (A) 8 European countries Fair	Double-blind, multicenter (27 centers)	16 -70 yrs with diagnosis of AD according to Hanifin and Rajka; required to have AD severity grading of moderate to severe according to Rajka and Langeland; disease involvement of at least 5% BSA. Exclusion: serious skin disorder other than AD that required treatemnt. Patients were not allowed: topical and systemic corticosteroids, antimicrobials and antihistamines, coal tar, topical nonsteroidal anti-inflammatory drugs, nonsteroidal immunosuppressants, UV light treatments (UVA and UVB), hypnotics and sedatives, and other investigational drugs.	NR	Tacrolimus 0.03-, 0.1%, and Hydrocortisone butyrate 0.1%; all were ointments applied twice daily x 3 weeks. Treatment to continue treatement for entire 3 weeks regardless of whether clearance was realized.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Reitamo, 2002 (A) 8 European countries Fair	Run-in: NR Washout: for prior treatments ranged from 5 days-6 weeks	Inhaled or intranasal corticosteroids were limited to 1 mg/d. Bath oil and nonmedicated emollients were allowed.	EASI, modified EASI, patient assessment of pruritus using 10-cm VAS, investigator's assessment of overall clinical improvement. Primary endpoint: mEASI mean AUC as a % of baseline. Baseline, days 3, 7, and weeks 2, 3 (and 2 weeks after completion of the	Mean age: 30.8-32.4 (SD 10.3-11.5) Female 53.2 - 57.1% White 94.8 - 97.8%

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Reitamo, 2002 (A) 8 European countries Fair	Median duration of AD: 23-25 yrs Median duration of current episode: 7.8-13.3 mos Moderate AD: 44.6-50.8% Severe AD: 49.2 - 55.4% Median affected BSA: 30-36.3% Affected body region: Head/neck: 93.3-95.8% Upper limbs: 98.4- 100% Trunk: 90.1 - 91.4% Lower limbs: 88.1 - 85.3%	NR NR 570	61 NR 559 (98.1%)

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Reitamo, 2002 (A) 8 European countries Fair	Change in mEASI from baseline (median % improvement) for tacro 0.03-, 0.1-, and hydrocort butyrate 0.1% oint: 53.0% vs. 63.5% vs. 63.9% (tacro 0.1- vs. 0.03%, p<0.001; tacro 0.1% vs. hydrocort butyrate, p-value= NSD; hydrocort butyrate vs. tacro 0.03%, p=0.002) For the Head/Neck, the median mEASI: similar findings to the above (data were not shown) Median % decrease in affected BSA: 60% vs. 78% vs. 79% (tacro 0.1- vs. 0.03%, p<0.05; hydrocort butyrate vs. tacro 0.03%, p<0.05) Findings for the EASI and pruritus were similar to those for the mEASI and affected BSA (data not shown). Physician's global evaluation of excellent/cleared: 37.6% vs. 49.2% vs. 51.4% (tacro 0.1% vs. hydrocort butyrate, p-value= NSD; tacro 0.1- vs. 0.03%, p<0.05; hydrocort butyrate vs. tacro 0.03%, p<0.05)	Investigator

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Reitamo, 2002 (A) 8 European countries Fair	Application site reactions for tacro 0.03-, 0.1, and hydrocort butyrate 0.1% oint: Skin burning: 45.1% vs. 59.2% vs. 12.9% Pruritus: 20.2% vs. 15.2% vs. 9.7% Folliculitis: 7.8% vs. 7.9% vs. 7.0% Skin erythema: 2.1% vs. 3.7% vs. 0.5% Macropapular rash: 0.5% vs. 2.6% vs. 1.1% Nonapplication site reaction: Flu syndrome: 4.1% vs. 6.3% vs. 6.5% Allergic reaction: 3.1% vs. 2.6% vs. 6.5% Headache: 5.2% vs. 4.7% vs. 7.5% Herpes simplex: 2.6% vs. 1.6% vs. 0.5% Infection AE that led to discontinuation were skin infection: 2 patients on hydrocort butyrate and 2 patients on tacro 0.1%) and herpes simplex infection (2 patients on tacro 0.03% and 1 patient on tacro 0.1%). No cases of eczema herpeticum were reported during the study. 4 additional patients had an AE that led to discontinuation: worsening of AD in hydrocort butyrate arm; urticaria, rash, and opthalmitis in tacro 0.03% arm	61 (10.7%) 18 (3.2%)	

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Reitamo, 2005 (A) 12 European countries Fair	Double-blind, multicenter (57 centers)	>18 yrs with AD according to Hanifin and Rajka criteria; required to have moderate to severe AD according to Rajka and Langeland (a score of at least 4.5). Prohibited therapies during the study included topical corticosteroids for the treatment of AD, systemic corticosteroids, systemic antimicrobials, sedating antihistamines, coal tar, ultraviolet (UV) radiation treatments, hypnotics and sedatives, and systemic immunosuppressive agents.	NR	Tacrolimus 0.1% vs. hydrocortisone acetate 1% (for head/neck)+ hydrocortisone butyrate 0.1% (trunk/extremities); all ointments applied twice daily x **6 mos** After clearance, leisons were to be treated for an additional 7 days. In the event of a flare, ointment application was to resume twice daily until clearance.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Reitamo, 2005 (A) 12 European countries Fair	Run-in: NR Washout: for prior treatments ranged from 5 days-6 weeks	Inhaled or intranasal corticosteroids were limited to 1 mg/d. Bath oil and nonmedicated emollients were allowed 2 hrs after study medication application.	Primary endpoint: the response rate at **3 mos** (defined as the % of patients with at least 60% improvement in mEASI score). Secondary endpoints: response rate at other time points like at 6 mos, mEASI, EASI, PGE, physician assessment of individual signs, % affected BSA, patient assessment of itch/sleep per 10-cm VAS, # of days (as a %) on treatment	32.1-32.9 yrs (SD 11.6-12) Female 53.8% White 95.5 - 97.5%

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Reitamo, 2005 (A) 12 European countries Fair	Duration of overall AD: mean 24.9-26.1 yrs (SD 13.1-13.7) Duration of current episode: mean 59.7-64.8 mo (SD 112.2 - 118.6); median 9.6-10.9 mo Mean total affected BSA: 0-25%: 38.6-39.6% >25-≤50%: 32.8-34.1% >50-≤75%: 17.7-18.6% >75-100%: 8.6-10.1% Affected body region: Head/neck: 93 - 93.4% Upper limbs: 98.6 - 98.8% Trunk: 86.9 - 91.8% Lower limbs: 85.2 - 90.5% Severity of AD: mild: 0; moderate: 56.1% -58.8%; severe: 41.2% - 43.9%	NR NR 972	328 NR 972* (unable to verify)

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Reitamo, 2005 (A) 12 European countries Fair	% of those who achieved at least 60% improvement in mEASI for tacrolimus and steroid at 3 mos: 72.6% vs. 52.3%, p<0.001 (95% CI 0.139-0.267); At 6 mos results were similar (estimated from graph) Median % change in mEASI from baseline to 6 mos for tacrolimus and vehicle: -87.7% vs. -82.5%, p<0.008 Median % change in EASI at 6 mos for tacrolimus and vehicle: -85.0% vs. -81.5% Meidan % change in affected total BSA: -88.2% vs. -80.3%, p=0.001 % who achieved clear or excellent at 6 mos: 61.3% vs. 46.4%, p<0.001 % of patients reporting better or much better improvement in clinical condition at 6 mos: 86.6% vs. 71.8%, p<0.001 Itch and qulaity of sleep were improved for patients in both treatment arms during the 6 mo period (data not shown)	Study investigators

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Reitamo, 2005 (A) 12 European countries Fair	Incidence of most common causally related AE for tacrolimus and steroid: Skin burning: 52.4% vs. 13.8%, p<0.001 Pruritus: 18.1% vs. 13.4% Lack of effect: 4.7% vs. 8.2%, p=0.027 Skin erythema: 4.9% vs. 3.7% Alcohol intolerance: 7.4% vs. 0.2%, p<0.001 Skin tingling: 2.7% vs. 0.6%, p=0.02 Hyperasthesia: 2.1% vs. 0.4%, p=0.037 Herpes simplex: 4.3% vs. 1.9%, p=0.04 (see Table 2 in trial for more details) Prevalence of application site skin burning over time for tacrolimus and steroid: week 1: 50.9% vs. 12.0% week 2: 17.3% vs. 4.6% month 3: 10.3% vs. 1.6% month 6: 6.6% vs. 0.7% Overall incidence of benign neoplasms and malignancies regardless of relationship to study drug for tacrolimus and steroid: Lymphadenopathy: 0.6% vs. 1.0% Begnin skin neoplasm: 0.4% vs. 0.4% Begnin neopasm: 0.4% vs. 0.0% Lymphoma-like reaction: 0.0% vs. 0.2% Skin carcinoma: 0.0% vs. 0.2%	328 (33.7%) 26 (2.7%)	

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Reitamo, 2004 (C) 11 European countries Fair	Double-blind, multicenter (42 centers)	2-15 yrs with AD according to Hanifin and Rajka criteria ; moderate to severe AD according to Rajka and Langeland; disease involvement of 5-100% of BSA. Prohibited therapies during the study included topical or systemic corticosteroids, antimicrobials and antihistamines, coal tar, topical nonsteroidal anti-inflammatory drugs, ultraviolet (UV) treatments (UVA and UVB), hypnotics and sedatives, and systemic immunosuppressive agents, e.g. ciclosporin.	NR	Tacrolimus 0.03% ointment once or twice daily, hydrocortisone acetate 1% ointment twice daily x 3 weeks.

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Reitamo, 2004 (C) 11 European countries Fair	Run-in: NR Washout: for prior treatments ranged from 5 days-6 weeks	Inhaled or intranasal corticosteroids were limited to 1 mg/day). Bath oil and nonmedicated emollients were permitted.	Primary endpoint: % change in mEASI Secondary endpoint: EASI, response rate, physician global evaluation, patient self assessment of disease, physician assessment of BSA involvement, patient's quality of sleep Baseline, days 1, 4, 8, and weeks 2, 3.	6.7 - 7.2 yrs (SD 3.9-4.2) Female: 48.3-54.8% White 81.9 - 86.5% Black 2.9-4.3% Asian 2.9 - 6.2%

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Reitamo, 2004 (C) 11 European countries Fair	Mean overall duration of AD: 5.7 - 6.3 yrs, (SD 3.8-4) Severity of AD Mild: 0.5% Moderate: 44.9-52.9% Severe: 46.7 - 55.1% Mean % affected BSA: 37.1 - 38.9% (SD 23.7-26)	NR NR 624	88 NR 624

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Reitamo, 2004 (C) 11 European countries Fair	Median % decrease in MEASI for tacrolimus Qday, Bid, and hydrocortisone acetate:70.0% vs. 78.7% vs. 47.2% (tacro Qday vs. hydrocortisone, p<0.001; tacro Bid vs. hydrocortisone, p<0.001; tacro Bid vs. tacro Qday, p=0.007) In general, the response rate (ie, at least 60% improvement) for those with severe disease was lower than for those with moderate disease at baseline; however, those with severe disease on BID tacro dosing had greater improvement than Qday dosing of tacro (75.5% vs. 54.1%, p=0.001). Median % decrease in EASI: 66.7% vs. 76.7% vs. 47.6%, p<0.001 tacro vs. hydrocortisone % affected BSA: data not shown; tacrolimus-treated patients had larger improvement than hydrocortison-treated patients (p<0.001) % achieving treatment success via physician's global assessment (ie, clear or excellent) for Qday, BID, hydrocortisone: 27.8% vs. 36.7% vs. 13.6% % of patient's reporting much better: 42.2% vs. 47.1% vs. 21.0% % of patient's reporting better or much better: 67.0% vs. 82.9% vs. 50.7% Change in pruritus score at week 3: -3 vs. -3.5 vs. -2 Change in quality of sleep at week 3: +1.6 vs. +2.5 vs. +1.4	NR

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Reitamo, 2004 (C) 11 European countries Fair	Incidence of most common AE irrespective of causality for tacro Qday-, BID-, and hydrocortisone acetate: Skin burning: 23.2% vs. 23.8% vs. 14.5% Pruritus 18.4% vs. 21.4% vs. 15.9% Skin erythema 2.9% vs. 2.9% vs. 1.0% Rash 1.4% vs. 2.9% vs. 1.0% (see Table 4 in trial for more details) Herpes simplex: 1.0% vs. 1.4% vs. 0.5% Kaposi's varicelliform: 0% vs. 0.5% vs. o% Flu and fever were the most common non-application site adverse events (data not shown)	88 17 (2.7%)	

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Comorbidities (other atopic-related ailments, infections, etc)?	Interventions
Schnopp, 2002 Germany Poor	Observer-blinded, single-center (university hospital, Dept of Dermatology and Allergy)	Moderate to severe chronic, relapsing dyshidrotic eczema. Exclusion: use of topical glucocorticoids or any systemic treatment with possible influence on course of disease (eg, steroids, antibiotics, antihistamines, nonsteroidal anti-inflammatory medications)	37.5% atopic (family history) 62.5% with contact allergies (esp with nickel)	Mometasone furoate 0.1% ointment twice daily, tacrolimus 0.1% ointment twice daily on the left or right plam or sole; the "second" medication was to be applied on the corresponding side x 4 weeks

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Run-in/Washout Period	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Mean age Gender Ethnicity
Schnopp, 2002 Germany Poor	Run-in: NR Washout: 2 weeks	Nonmedicated emollients	Dyshidrotic eczema area and severity index (DASI) score. Baseline, after 2 weeks, after 4 weeks of active treatment.	43 yrs Female: 93.8% Ethnicity: NR

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Schnopp, 2002	Mean duration of disease: 38.6 mo.	NR	0
Germany		20	0
Poor	History of atopic disease: 37.5%	16	16
	Contact allergies, including nickel: 62.5% Nickel sensistization: 37.5%		
	Previous phototherapy: 56.6%		
	Palms affected: 75% Soles affected: 25%		

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment
Schnopp, 2002 Germany Poor	% reduction in DASI score for mometasone and tacrolimus (Palmar region): 50% vs. 50%, p=NSD After 4 weeks, tacrolimus treated areas tended to worsen slightly compared with 2-week score whereas mometasone treated areas remained stable (Palmar regions). Plantar regions: DASI scores remained almost unchanged during treatment with tacrolimus compared with mometasone (change in DASI score: +2.8 vs. -11.5)	NR

Evidence Table 11. Active-controlled trials of tacrolimus

Author Year Country Trial Name (Quality Score)	Adverse events	Total withdrawals; withdrawals due to adverse events	Comments
Schnopp, 2002 Germany Poor	NR	0 0	AE were not reported

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Bieber, 2007 Germany, Italy, Spain	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Torok, 2003 NR	Method not described	Method not described	Unable to determine; data were not provided for each arm	Yes	Yes	No
Hung, 2007 Taiwan	Method not described	Method not described	No, differences in age, gender, and overall SCORAD scores at baseline among the arms.	Yes	No	No
Reitamo, 2002 (C) Europe, Canada	Yes, randomization number list supplied by the sponsor (central)	Yes, sequentially ordered numbers provided by the sponsor	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Reitamo, 2002 (A) Europe	Yes, randomization number list supplied by the sponsor (central)	Yes, sequentially ordered numbers provided by the sponsor	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Reitamo, 2005 (A) Europe	Yes, randomization number list supplied by the sponsor (central)	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Bieber, 2007 Germany, Italy, Spain	Yes, MPA patients received vehicle to maintain blinding; both arms received 2-tubes of ointment	Adherence- Yes by weighing tubes to measure usage	Yes/No	Yes, missing data was classified under "no success" for IGA score; LOCF was used for secondary endpoints	No	Fair
Torok, 2003 NR	No	NR NR NR	NR/NR	Yes; unclear how missing data were handled	No	Poor
Hung, 2007 Taiwan	No	Yes NR NR NR	No/No	Unable to verify if ITT; also unclear how missing data were handled	No	Poor
Reitamo, 2002 (C) Europe, Canada	Yes, identical tubes were provided	Yes NR NR NR	No/No	Yes, unclear how missing data were handled	No	Fair
Reitamo, 2002 (A) Europe	Yes, identical tubes were provided	Yes NR NR NR	No/No	Yes, unclear how missing data were handled	No	Fair
Reitamo, 2005 (A) Europe	Yes, identical tubes were provided	Yes NR Yes NR	Yes, differential (25.5% tacrolimus vs. 42.1% steroid) Yes (33.7% total)	Yes, missing data classified as nonresponders	No	Fair

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Funding
Bieber, 2007 Germany, Italy, Spain	Intendis, GmbH (manufacturer of MPA)
Torok, 2003 NR	NR
Hung, 2007 Taiwan	NR
Reitamo, 2002 (C) Europe, Canada	Fujisawa GmbH
Reitamo, 2002 (A) Europe	Fujisawa GmbH
Reitamo, 2005 (A) Europe	Fujisawa GmbH

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Reitamo, 2004 (C) Europe	Method not described	Method not described	Slighlty more patients in the hydrocortisone acetate arm had severe disease compared with the other treatment arms	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Schnopp, 2002 Germany	Method not described	Method not described	Unable to determine; data were not provided for each arm	Yes	Yes	Unknown, reported as observed-blind

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Withdrawals: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Reitamo, 2004 (C) Europe	Yes	Yes NR NR NR	Yes, differential (10-12.6% tacrolimus vs. 19.8% hydrocortisone) No (14.1% total)	Yes, but unclear how missing data were handled	No	Fair
Schnopp, 2002 Germany	Unknown, reported as observer-blind	Yes NR NR NR	No/No	Yes, but unclear how missing data were handled	No	Poor

Evidence Table 12. Quality assessment of active-controlled trials of tacrolimus

Author, Year Country	Funding
Reitamo, 2004 (C) Europe	Fujisawa GmbH
Schnopp, 2002 Germany	None

Evidence Table 13. Observational studies of topical calcineurin inhibitors

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size
Arellano, 2007 US	Nested, case-control	To assess the risk of lymphoma associated with the use of topical prescription treatments for atopic dermatitis	Obtained data from July 1995-January 2005; however, most (75%) of patients were enrolled in the database from 2001 onwards	PharMetrics database which includes data from 43 million US patients from 73 health care plans	Patients with atopic dermatitis in PharMetrics= 502,283 After applying inclusion and exclusion criteria, sample N= 293,253

Evidence Table 13. Observational studies of topical calcineurin inhibitors

Author, year Country	Population characteristics	Statistical methods	Effectiveness outcomes
Arellano, 2007 US	Cases and controls were identified using ICD-9 codes. Cases of lymphoma were reviewed by blinded hematologists. 58.6% were < 20 years old; atopic dermatitis was mainly diagnosed by family physician, pediatrician, or dermatologist; 20% of patients had severe disease; At index date 25% of patients used topical steroids vs. 1.5-3% of patients on topical calcineurin inhibitors; 12% of patients were exposed to at least 1 topical calcineurin inhibitor Inclusion: at least 6 months enrollment in the database Exclusion: diagnosis of lymphoma, cancer, immunosuppression, transplant, HIV/AIDS, on immunosuppressant agents, on anti-cancer agents before index date	Used logistic regression conditional on case sets with similar duration of follow-up to calculate OR and 95% CI.Final model was adjusted for all confounders. Adjusted for age, sex, region, medical specialty at atopic dermatitis diagnosis, presence of infectious mononucleosis, use of asthma medications, oral steroid use, severity of disease	NR and N/A

Evidence Table 13. Observational studies of topical calcineurin inhibitors

Author, year Country	Safety Outcomes	Comments	Funder
Arellano, 2007 US	A total of 294 cases of lympma were identified after the index date; 81 (27.6%) occurred in aptients <20 years of age. No. of cases of lymphoma for patients exposed to: Pimecrolimus= 14 Tacrolimus= 11 Both= 5 Type of lymphoma could not be determined for 66% of cases. Among those identified: Hodgkin=11.2%; NHL=22.8%; T-cell NHL=18.4%; B-cell NHL=4.4% Risk of lymphoma after adjusting for confounders: Pimecrolimus: OR 0.8 (95% CI, 0.4-1.6) Tacrolimus: OR 0.8 (95% CI, 0.4-1.7) Low potency topical steroid: OR 1.1 (95% CI, 0.7-1.6) High potency topical steroid: OR 1.2 (95% CI, 0.8-1.8) High exposure to topical steroid and/or topical calcineurin inhibitor: OR 2.3 (95% CI, 1.17-4.51) Severe atopic dermatitis: OR 2.4 (95% CI, 1.5-3.8) Use of oral steroids: OR 1.5 (95% CI, 1.0-2.4)	Index date-the day a code for atopic dermatits was first preented in the database Authors report that their database did not capture the frequency and extent of use of over-the-counter topical agents (eg, emollients, low potency topical steroid, etc). Main limitation was the inability to validate information obtained by record linkage in PharMetrics; thus, unable to ascertain the degree of missclassification that may have occurred.	Novartis

Evidence Table 13. Observational studies of topical calcineurin inhibitors

Author, year Country	Study design	Study objective	Time period covered	Data source	Sample size
Margolis, 2007 US (Single center, Dept of Dermatology at the Univ of Pennsylvannia)	Nested, case-control	To investigate whether adults, who are already at higher risk of developing nonmelanoma skin cancer (NMSC) than children, who used topical calcineurin inhibitors (TCI) in the past few years were more likely to develop NMSC than those who did not use TCIs.	2002-2005	Self-administered questionnaire written in English was mailed to potential cases and controls. The authors did not explicity report which data source was used to identify cases and controls. We assume medical records from dermatology clinic at the Univ of Pennsylvannia were used.	Total sample size was not reported but 5,000 eligible study subjects (who were "randomly" selected based on ICD-9 codes) were identified after meeting inclusion/exclusion criteria. Survey questionnaires were mailed to 5,000 patients. 51 patients died and 107 subjects no longer had deliverable addresses. 3,074 surveys were returned completed (63.5%) which includes: 2394 surveys from the control group (61.9%) + 680 surveys from the case group (69.6%); 253 patients were excluded because of a reported history of organ transplantation or use of oral immunosuppressive agents. 2,821 subjects (56.4%) of the original 5,000 patients were evaluated for this study. This reclassification yields a total of 1946 control and 875 case subjects.

Evidence Table 13. Observational studies of topical calcineurin inhibitors

Author, year Country	Population characteristics	Statistical methods	Effectiveness outcomes
Margolis, 2007 US (Single center, Dept of Dermatology at the Univ of Pennsylvania)	35.4% of subjects in the control group were male vs. 55.0% in the case group The prevalence of self-reported history of atopic dermatitis was 8.9% among cases and 18.9% among controls. Overall, 25.7% (710 of 2763 subjects) reported exposure to TCIs. The prevalence of TCI exposure was 14.4% among cases and 30.7% among controls. There were statistically significant differences in certain patient characteristics between those in the case cohort compared with control cohort. The characteristics included: gender, age, history of NMSC before 2002, history of atopic dermatitis, history of being easy to sunburn, history of any ETOH use, history of cigarette use. Eligible subjects were >30 yrs of age and was originally diagnosed as having "dermatitis" (which includes seborrheic dermatitis, dermatitis NOS, rosacea, etc). The borader criteria of "dermatitis was selected to reflect "real world" exposure because TCIs are used in adults off-label for inflammatory skin disease other than AD. Subject initially referred to the Dept of Dermatology (prior to a diagnosis by a faculty member for dermatitis) for treatment or evalua *There was no report of duration of TCI usage or duration of disease	For primary analysis, unadjusted and adjusted associations were estimated by bivariable and multivariable logistic regression for TCI exposure among those with and without NMSC. Confounders that were selected for use in the adjusted models included those that either changed the unadjusted assoc bw the markers for atopic dermatitis and skin cancer by >15% or were deemed by the study team to be clinically relevant. Several secondary and sensitivity analyses were also performed	NR and N/A

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Author, year Country	Safety Outcomes	Comments	Funder
Margolis, 2007 US (Single center, Dept of Dermatology at the Univ of Pennsylvania)	Odds rations as estimated using logistic regression of exposure with 95% CI: TCI for the full case-control study: unadjusted OR 0.38 (0.31-0.47) adjusted OR 0.54 (0.41-0.69) TCI among those with a history of atopic dermatitis: unadjusted OR 0.42 (0.24-0.72) adjusted OR 0.50 (0.25-0.98)	*No report of duration of exposure to TCI, duration of illness, or severity of illness	Novartis

Evidence Table 14. Quality assessment of topical calcineurin inhibitors

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**
Arellano, 2007	Unclear, patients with <6 months enrollment in the data were exlcuded (see also inclusion/exclusion criteria)	N/A	Yes	Yes	Yes

Evidence Table 14. Quality assessment of topical calcineurin inhibitors

Author Year	Statistical analysis of potential confounders?	Mean duration of follow-up	Adequate duration of follow-up?	Overall quality rating	Comments
Arellano, 2007	Yes (adjusted for confounders)	NR	No	Fair	Authors report that their database did not capture the frequency and extent of use of over-the-counter topical agents (emollients, low potency topical steroid, etc). The main limitation was the inability to validate information obtained by record linkage in PharMetrics; thus, unable to ascertain the degree of missclassification that may have occurred.

Evidence Table 14. Quality assessment of topical calcineurin inhibitors

	Internal validity				
Author Year	**Non-biased selection?**	**Loss to follow-up specified? If yes, low overall loss to follow-up?**	**Outcomes pre-specified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**
Margolis, 2007	Unclear, authors report cases were "randomly selected" based on additional visit evaluation between 2002-2005 with ICD-9 codes used to designate NMSC. *Note: It was unclear whether 5,000 "eligible" subjects represented ALL patients (N=?) who were eligible for the study before applying inclusion/exclusion criteria, or if this cohort represented patients that met all inclusion/exclusion criteria.	Yes, "loss to follow-up" was reported, however, there was significant difference in the final cohort compared to the eligible cohort. Of the 5,000 eligible study subjects (4,000 control and 1,000 cases): 2,821 subjects were evaluated for this study (56.4%). 1,946 control (48.7%) and 875 cases (87.5%) were evaluated.	Yes	Yes	High potential for recall bias. Authors did not report what measures they took to try and minimize this bias. Patients were mailed questionnaires written in English and it is unclear whether any additional follow-up by phone or mail were made.

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Author Year	Statistical analysis of potential confounders?	Mean duration of follow-up	Adequate duration of follow-up?	Overall quality rating	Comments
Margolis, 2007	Yes (adjusted for confounders)	NR	NR	Poor	Potential for significant recall bias and no explanation of its limitations; unknown mean duration of follow-up; unclear identification of total sample population (what was N?, was it 5,000 subjects or >5,000 subjects?); significant difference in final cohort vs. "initial" sample; unknown duration of exposure to TCI; unknown area of application.