Title

Study of the Atopic March: Development of Atopic Comorbidities

Journal

Pediatric Dermatology, 33(4)

ISSN

0736-8046

Authors

Schneider, Lynda
Hanifin, Jon
Boguniewicz, Mark
et al.

Publication Date

2016-07-01

DOI

10.1111/pde.12867

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Dermatol. Author manuscript; available in PMC 2017 October 20.

Published in final edited form as:

Pediatr Dermatol. 2016 July ; 33(4): 388–398. doi:10.1111/pde.12867.

Study of the Atopic March: Development of Atopic Comorbidities

Lynda Schneider, M.D.[*], **Jon Hanifin, M.D.**[†], **Mark Boguniewicz, M.D.**[‡,¶], **Lawrence F. Eichenfield, M.D.**[#], **Jonathan M. Spergel, M.D., Ph.D.**[**], **Rada Dakovic, Ph.D.**[††], and **Amy S. Paller, M.D.**[‡‡]

[*]Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts

[†]Oregon Health and Science University, Portland, Oregon

[‡]National Jewish Health, University of Colorado, Denver, Colorado

[¶]School of Medicine, University of Colorado, Denver, Colorado

[#]Rady Children's Hospital, San Diego, California

[**]Division of Allergy and Immunology, Children's Hospital of Philadelphia and Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[††]Meda Pharma GmbH & Co. KG, Bad Homburg, Germany

[‡‡]Ann and Robert H. Lurie Children's Hospital of Chicago and Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Abstract

Background—Atopic dermatitis (AD) is often the first step in the atopic march leading to the development of asthma or allergic rhinitis. The goal of this study was to determine whether early intervention with pimecrolimus limits the atopic march in infants with AD and to evaluate its efficacy and safety.

Methods—This was a 3-year double-blind study in which patients were randomized to pimecrolimus or vehicle and then open-label pimecrolimus for a planned further 3 years. Rescue topical corticosteroid was permitted if 3 days of study medication led to no improvement; investigators made decisions on rescue medication until week 14 and caregivers thereafter. Efficacy assessments included disease-free days, Eczema Area and Severity Index, and body surface area affected.

Results—Infants ages 3 to 18 months with recent-onset AD (≤3 months) were observed for a mean of 2.8 years (N = 1,091). No significant differences between pimecrolimus- and placebo-treated groups were found in the percentage of patients with AD who developed asthma (10.7%)

Address correspondence to Amy S. Paller, M.D., Department of Dermatology, 676 N. St. Clair, Suite 1600, Chicago, IL 60611, or apaller@northwestern.edu.

CONFLICT OF INTEREST

All authors except Rada Dakovic were past investigators for Novartis. Lynda Schneider is an investigator for Astellas. Jon Hanifin is a consultant with honorarium for Novartis and an investigator for Astellas. Lawrence F. Eichenfield is an investigator for Astellas, a consultant with honorarium for Valeant, and a past consultant with honorarium for Novartis. Jonathan M. Spergel is a consultant with honorarium for Novartis, Dannone, and DBV Technologies. Rada Dakovic is a Meda Pharma employee. Amy S. Paller is a consultant with honorarium for Novartis and an investigator for Astellas.

or other allergic conditions (allergic rhinitis, 22.4%; food allergy, 15.9%; allergic conjunctivitis, 14.1%; one or more atopic comorbidities, 37.0%) by study end. Allergic rhinitis, food allergy, and having one or more atopic comorbidities (but not asthma or allergic conjunctivitis alone) developed significantly more often in infants with greater AD severity at baseline. Pimecrolimus was significantly more effective than vehicle for AD treatment at week 14. Adverse event incidences were similar.

Conclusions—This longitudinal observation of infants with AD provides evidence of the atopic march. Pimecrolimus was safe and effective in infants with mild to moderate AD.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, relapsing, pruritic skin disorder that is common during infancy and childhood (1). It is often the first step in the atopic march leading to the development of asthma or allergic rhinitis (2). Early and effective treatment of AD could theoretically interrupt the atopic march and decrease the risk of asthma (3).

Pimecrolimus 1% cream, a topical calcineurin inhibitor, is safe and effective for treating AD in infants (4–9). The Study of the Atopic March (SAM) aimed to prospectively investigate whether early intervention with pimecrolimus was able to limit the atopic march and, in particular, reduce the risk of developing asthma in a large population of U.S. infants with AD and effectively treat AD as assessed using well-established parameters (Eczema Area and Severity Index (EASI), body surface area involved). SAM established a large database of infants with AD who were prospectively assessed for the development of allergic comorbidities. The study provides longitudinal data about the atopic march and, given the large size of this cohort, makes a major contribution to understanding of the safety of pimecrolimus in infants with AD.

MATERIALS AND METHODS

Patients

Infants ages 3 to 18 months with an AD diagnosis (American Academy of Dermatology Consensus Conference criteria (10)), clinical evidence of AD of 3 months or less duration, a family history of atopy (one or more parents or siblings), and at least mild AD (Investigator Global Assessment [IGA] score of 2 or greater; 0 = clear, 5 = very severe) were eligible. Patients receiving topical tacrolimus or any topical agent with a possible effect on AD within 7 days, daily treatment with antihistamines, or other systemic therapy (e.g., immunosuppressive medications, leukotriene antagonists) within 1 month before first study drug application were excluded. Legal guardians of eligible patients provided written informed consent.

Study Design

SAM (NCT00124709) was conducted from October 2003 to November 2008 in accordance with the principles of the Declaration of Helsinki (2002). The Institutional Review Board for each center approved the study protocol.

In the initial 3-year double-blind phase of SAM, eligible patients were randomized 1:1 to pimecrolimus or vehicle (identical appearance and odor). Patients without a definitive diagnosis of asthma continued into the open-label phase for as-needed treatment with pimecrolimus for 3 years or until 6 years of age, whichever came first. A stepwise approach to AD treatment was used in which disease severity dictated treatment choice (Fig. 1). Rescue therapy with topical corticosteroid (TCS; fluticasone propionate 0.05% cream; referred to as Treatment Step 3a) was permitted if 3 days of study medication led to no improvement, with investigators making decisions until week 14 and caregivers thereafter (training provided at the randomization visit). Daily application of emollients on healthy and inflamed skin was encouraged. Twelve study visits were scheduled in the double-blind phase and a maximum of six visits in the open-label phase.

Data Collection

Primary caregivers recorded evidence of active AD, number of affected body areas (range 0–24), severity of erythema (scale 0–3) and pruritus (scale 0–3), treatment used (including rescue TCS), and symptoms of suspected noncutaneous atopic conditions, including food allergy, allergic rhinitis, allergic conjunctivitis, and asthma, in an electronic diary once daily to weekly (summary data entry permitted caregivers to record data for up to 126 days). Investigators reviewed the e-diary records and discussed them with caregivers. Diagnoses of asthma (11,12), food allergy (13), allergic rhinitis (14), and allergic conjunctivitis (14) were made using standard criteria.

Investigator assessments of efficacy included IGA of disease severity, total body surface area (TBSA) affected (0–100%), total EASI score (0–72 scale), and subscores according to body region (head and neck, upper limbs: 0–14 scale; trunk, lower limbs: 0–22 scale). Adverse events (AEs) were recorded throughout the study.

Efficacy Endpoints

Three coprimary efficacy variables were based on caregiver-provided e-diary data: proportion of disease-free days in Treatment Step 2 (pimecrolimus or vehicle) or Treatment Step 1 (emollient only; Fig. 1), proportion of disease-free days in Treatment Step 1 only, and longest duration of remission. The fourth coprimary efficacy variable was percentage of patients diagnosed with asthma by 6 years of age.

Secondary efficacy variables were (i) change from baseline in total EASI score; (ii) change frombaseline in TBSA affected; (iii) number of days of rescue treatment (Treatment Steps 3a, 3b, 4); percentage of patients with (iv) food allergy, (v) allergic rhinitis, (vi) allergic conjunctivitis, and (vii) one or more atopic comorbidities (post hoc analysis); mean (viii) pruritus and (ix) erythema scores; (x) number of affected body areas; and (xi) percentage of patients with an IGA of 0 or 1.

The protocol specified that the study be discontinued if coprimary efficacy variables did not reach statistical significance. SAM was terminated early based on an independent advisory board recommendation after review of the double-blind phase results.

Statistical Methods

Approximately 1,100 randomized patients (550 per treatment group) were required for efficacy analyses based on the percentage of patients diagnosed with asthma by 6 years of age (30% in the pimecrolimus group, 45% in the and control group). An allocation ratio of 1:1, a two-sided *Z*-test with a continuity correction, a two-sided significance level of 0.05, and statistical power of 0.90 provided a total sample size of 460 patients. Incorporating a dropout rate of 0.35, it was determined that approximately 708 patients were needed. Further, by considering patients who dropped out as having been diagnosed with asthma by 6 years of age, approximately 1,100 patients (≈708/[1–0.35]) were to be randomized (15,16).

Statistical analyses were performed using SAS versions 8.2 and 9.2 (SAS Institute, Cary, NC). All statistical tests were conducted against a two-sided alternative hypothesis using a 0.05 significance level. The safety population included all randomized patients who were dispensed study medication. The intent-to-treat (ITT) population included all randomized patients who were dispensed study medication and had one or more postbaseline efficacy measurements.

The first three coprimary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model with treatment, center, sex, baseline age, baseline total EASI score, and baseline TBSA affected as explanatory variables; secondary analyses of these variables were performed using the van Elteren test, adjusting for center and sex (17). Secondary efficacy variables i through iii and viii through x were analyzed using the ANCOVA model (and the van Elteren test for variable iii). Secondary efficacy variables iv through vii and the percentage of patients with asthma were analyzed at double-blind and open-label treatment phase completion using the Cochran–Mantel–Haenszel test, adjusting for baseline IGA, center, and age, as was secondary efficacy variable xi up to double-blind phase completion, adjusting for center and sex (17). An exploratory post hoc analysis evaluated the proportion of patients who developed atopic comorbidities according to their baseline AD severity (IGA 1 or 2 vs ≥3) using logistic regression with treatment, sex, and baseline IGA severity subgroup.

RESULTS

Patients

A total of 1,091 patients were randomized in this study: 546 to pimecrolimus and 545 to control (Fig. 2). Of these, 469 entered the open-label phase. The mean follow-up was 2.8 years for the entire study and 1.2 years for the open-label phase. The treatment groups had similar baseline characteristics. Most patients were 3 to 12 months of age, and approximately half had mild AD (Table 1).

Of the 497 patients who withdrew consent ($n = 263$) or were lost to follow-up ($n = 234$) during the double-blind phase, 44% left the study between February 2005, when the U.S. Food and Drug Administration first considered a boxed warning for pimecrolimus, and early 2006, when the warning was implemented. Comparing characteristics of patients who did and did not complete the double-blind phase showed that a greater proportion of completers

were Caucasian and a lower proportion were black in both treatment groups. Furthermore, a greater proportion of completers treated with pimecrolimus had moderate disease (45.7%) than of those treated with control (35.2%; Table 1).

Atopic Comorbidities

Of infants in the ITT population (n = 1,065), 9.5% developed asthma and 33.3% one or more atopic comorbidities (allergic rhinitis, food allergy, allergic conjunctivitis, asthma) by the end of the double-blind phase (Table 2). By study end, 10.7% had developed asthma and 37.0% one or more atopic comorbidities. No significant differences between the pimecrolimus- and placebo-treated groups were found in the percentage of patients who developed asthma (9.5%) or other allergic conditions (allergic rhinitis, 18.5%; food allergy, 14.9%; allergic conjunctivitis, 11.9%, one or more atopic comorbidities, 33.3%) during the 3-year double-blind period, after correcting for baseline severity, center, and age (Table 2 and Fig. 3A). A significantly greater percentage of pimecrolimus-treated patients developed one or more atopic comorbidities after correcting for center and age only (data not shown). Similar results were observed in an analysis of patients who completed the double-blind phase of the study (n = 564), although the percentage of patients with asthma (13.8%), other individual atopic conditions (17.2%–25.9%), or one or more atopic comorbidities (46.6%) was higher than in the ITT population (Table 2). Allergic rhinitis, food allergy, and having one or more atopic comorbidities, but not asthma or allergic conjunctivitis, developed more often in the double-blind phase and during the entire study in children with greater baseline AD severity (Table 2 and Fig. 3B). The mean age ± standard deviation at onset of atopic comorbidities was 1.8 ± 1.0 years for food allergy, 2.2 ± 1.1 years for asthma, 2.3 ± 1.3 years for allergic conjunctivitis, and 2.4 ± 1.3 years for allergic rhinitis.

Efficacy

Pimecrolimus was significantly more effective than vehicle for treating AD at week 14, when investigators were deciding about rescue treatment initiation (Table 3). By the next assessment (week 27, when caregivers had been deciding about initiating TCS rescue for 13 weeks) through the end of the double-blind phase, few significant differences between the treatment groups were evident. EASI scores for the head and neck remained significantly better for the pimecrolimus group throughout the double-blind phase. Fewer steroid-rescue days were required during the double-blind phase for pimecrolimus than for controls (median 32 vs 49 days; p = 0.20 from ANCOVA, p = 0.002 from van Elteren test).

Safety

AEs and serious AEs occurred at similar frequencies in the two treatment groups (Table 4). Most AEs were mild and were infections or atopic conditions.

DISCUSSION

SAM provides longitudinal data about the atopic march and development of atopic comorbidities in more than 1,000 infants with AD, 54% of them followed for 3 years or longer, with 32% of those followed for 4 years or longer. The study further confirms the efficacy and safety of early intervention with pimecrolimus that has been seen in other short-

and long-term investigations; most recently, the Petite study showed no effect on immune system development during the first 5 to 6 years of life (4–9). SAM provides valuable information about the prevalence of developing atopic comorbidities in a large, well-studied patient base. Approximately 11% of the 1,091 infants (mean age 3.4 years at study end) developed asthma, 14% to 22% developed other atopic conditions, and the development of allergic rhinitis and food allergy correlated with baseline AD severity, providing evidence of the atopic march.

The rates of atopic comorbidities observed in SAM are lower than those reported in other studies. For example, a systematic review of eczema cohort trials reported an asthma prevalence of 29.5% at age 6 years (18). In a cross-sectional study of 2,270 children with AD, 66% had one or more atopic comorbidities by age 3 years (19). The lower rates of asthma and other atopic conditions in SAM could be due to study treatment interventions or that patients mainly had mild to moderate disease, given the putative link between AD severity and the development of atopic comorbidities (20). The nonsignificantly marginally higher incidence of asthma in the pimecrolimus group may have resulted from the slightly higher proportion at baseline of patients with moderate AD than in the control group. The temporal order of onset of atopic comorbidities (food allergy, then asthma, then allergic rhinitis) was in agreement with previous observations (21).

The unexpectedly high discontinuation rate (48%) dramatically reduced the power of this investigation in addressing whether pimecrolimus affected the atopic march. Given the long duration of the double-blind arm, we allowed rescue with fluticasone, one of the few topical corticosteroids indicated for infants with AD at the time of study design. This early initiation of a midpotency TCS after only 3 days of pimecrolimus, coupled with empowering caregivers to decide on the need for rescue, may have obscured differences in allergic comorbidities and other efficacy endpoints.

The findings of SAM suggest that long-term studies in AD should have simpler designs, with treatment decisions by investigators rather than caregivers. Investigations to determine whether early and aggressive antiinflammatory topical intervention decreases or delays the occurrence of the atopic march, or diminishes the severity of atopic comorbidities, are challenging because of the ethical imperative to treat infants with this uncomfortable, life-altering disorder.

Acknowledgments

We thank the SAM study investigators: William Berger (Southern California Research, Mission Viejo, CA), Mark Boguniewicz (National Jewish Medical & Research Center, Denver, CO), John Calcagno (Calcagno Research and Development, Gresham, OR), Bradley Chipps (Capital Allergy and Respiratory Disease Center, Sacramento, CA), Bernard Cohen (Johns Hopkins University Hospital, Baltimore, MD), Fernando de Castro (Central Kentucky Research, Lexington, KY), James Dinulos (Dartmouth–Hitchcock Medical Center, Lebanon, NH), Lawrence Eichenfield (Children’s Hospital, San Diego, CA), Mark Ellis (Children’s Hospital of Orange County, Orange, CA), David Fivenson (Ann Arbor, MI), Joseph Fowler (Dermatology Specialists, Louisville, KY), Michael Gold (Tennessee Clinical Research Center, Nashville, TN), Jon Hanifin (Oregon Health and Science University Center for Health & Healing, Portland, OR), Joshua Jacobs (Allergy and Asthma Clinical Research, Walnut Creek, CA), Stephen Kimura (Emerald Coast Clinical Research, Pensacola, FL), Toan Lam (Wasatch Clinical Research, Salt Lake City, UT), Alfred Lane (Stanford University Department of Dermatology, Stanford, CA), Craig Leonardi (Central Dermatology, St. Louis, MO), Herschel P. Lessin (Children’s Medical Group, Poughkeepsie, NY), Moise Levy (Texas Children’s Hospital, Houston, TX), Amy Paller (Children’s Memorial Hospital, Chicago, IL), Sean Livingston (Northwest Arkansas Pediatric Clinic, Fayetteville, AR), David Pariser (Virginia Clinical Research,

Norfolk, VA), Mark Pittelkow (Mayo Clinic, Rochester, MN), Louisa Randall (Radiant Research, West Valley City, UT), Joel Schlessinger (Skin Specialists, Omaha, NE), David Rodriguez (Dermatology Associates and Research, Coral Gables, FL), David Schneider (Rx R&D, Metairie, LA), Lynda Schneider (Children's Hospital, Boston, MA), Nanette Silverberg (Dermatology Associates of St. Luke's –Roosevelt, New York, NY), Phyllis Skaug (Children's Clinic of Jonesboro, PA), David Skoner (Allegheny General Hospital, Pittsburgh, PA), Carol Smith (Alabama Allergy and Asthma Center, Birmingham, AL), Jonathan Spergel (Children's Hospital of Philadelphia, Philadelphia, PA), Stephen Tilles (A.S.T.H.M.A., Seattle, WA), Patricia Treadwell (Indiana University Outpatient Clinical Research, Indianapolis, IN). We thank David Harrison, of Medscript, for providing editorial assistance, which was funded by Meda Pharma.

References

1. Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011; 131:67–73. [PubMed: 20739951]
2. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Asthma Immunol. 2010; 105:99–106. [PubMed: 20674819]
3. Galli E, Gianni S, Auricchio G, et al. Atopic dermatitis and asthma. Allergy Asthma Proc. 2007; 28:540–543. [PubMed: 18034972]
4. Paul C, Cork M, Rossi AB, et al. Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Pediatrics. 2006; 117:e118–e128. [PubMed: 16361223]
5. Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. Pediatrics. 2015; 135:597–606. [PubMed: 25802354]
6. Kapp A, Papp K, Bingham A, et al. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. J Allergy Clin Immunol. 2002; 110:277–284. [PubMed: 12170269]
7. Ho VC, Gupta A, Kaufmann R, et al. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. J Pediatr. 2003; 142:155–162. [PubMed: 12584537]
8. Kaufmann R, Folster-Holst R, Hoger P, et al. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. J Allergy Clin Immunol. 2004; 114:1183–1188. [PubMed: 15536429]
9. Papp KA, Werfel T, Folster-Holst R, et al. Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. J Am Acad Dermatol. 2005; 52:240–246. [PubMed: 15692468]
10. Eichenfield LF, Hanifin JM, Luger TA, et al. Consensus conference on pediatric atopic dermatitis. J Am Acad Dermatol. 2003; 49:1088–1095. [PubMed: 14639390]
11. Warner JO. A double-blinded, randomized, placebo-controlled trial of cetirizine in preventing the onset of asthma in children with atopic dermatitis: 18 months' treatment and 18 months' posttreatment follow-up. J Allergy Clin Immunol. 2001; 108:929–937. [PubMed: 11742270]
12. ETAC Study Group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: first results of ETAC. Early Treatment of the Atopic Child Pediatr Allergy Immunol. 1998; 9:116–124. [PubMed: 9814724]
13. Thompson MM, Tofte SJ, Simpson EL, et al. Patterns of care and referral in children with atopic dermatitis and concern for food allergy. Dermatol Ther. 2006; 19:91–96. [PubMed: 16669991]
14. Leung, DYM., Sampson, HA., Geha, RS., et al. Pediatric Allergy—Principles and Practice. 2. St. Louis: Mosby; 2003.
15. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Control Clin Trials. 1981; 2:93–113. [PubMed: 7273794]
16. Donner A. Approaches to sample size estimation in the design of clinical trials—a review. Stat Med. 1984; 3:199–214. [PubMed: 6385187]
17. Stokes, ME., Davis, CS., Koch, CG. Categorical Data Analysis Using the SAS System. 2. Cary, NC: SAS Institute; 2000.
18. van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. J Allergy Clin Immunol. 2007; 120:565–569. [PubMed: 17655920]

19. Kapoor R, Menon C, Hoffstad O, et al. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. J Am Acad Dermatol. 2008; 58:68–73. [PubMed: 17692428]
20. Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol. 2014; 5:202. [PubMed: 25419479]
21. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003 Dec; 112(6 Suppl):S118–S127. [PubMed: 14657842]

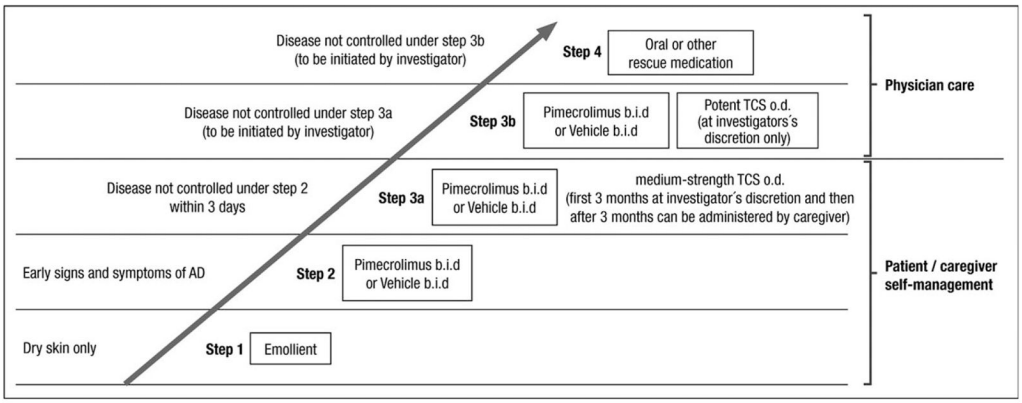

Figure 1.

Dose escalation scheme. All patients received emollient only during Treatment Step 1. During Treatment Step 2, patients were randomized 1:1 to twice-daily pimecrolimus 1% or vehicle-only cream. Patients received add-on once-daily TCS in Treatment Step 3a (medium strength) or Treatment Step 3b (potent). With severe disease exacerbations, an oral agent was used in Treatment Step 4. AD, atopic dermatitis; TCS, topical corticosteroid.

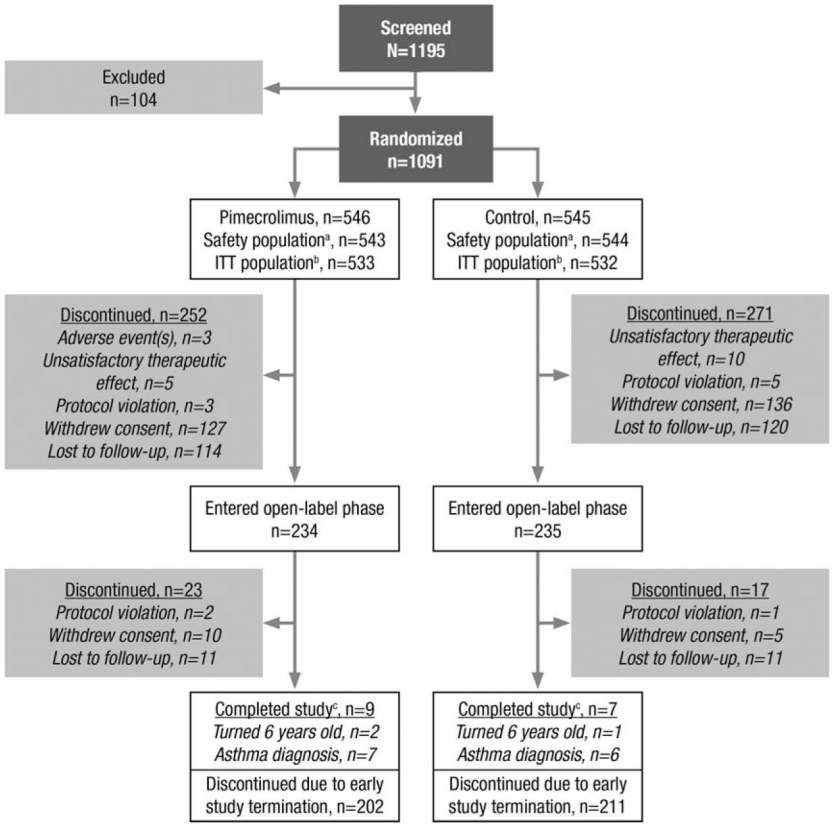

Figure 2.

Patient disposition. *Safety population included all randomized patients who were dispensed study medication. †Intent-to-treat (ITT) population included all randomized patients who were dispensed study medication and had one or more postbaseline efficacy measurements. ‡Study was terminated early based on independent scientific advisory board recommendation of the double-blind phase results (i.e., the proportion of disease-free days in Treatment Step 2 [pimecrolimus or vehicle] or Step 1 [emollient] did not reach statistical significance).

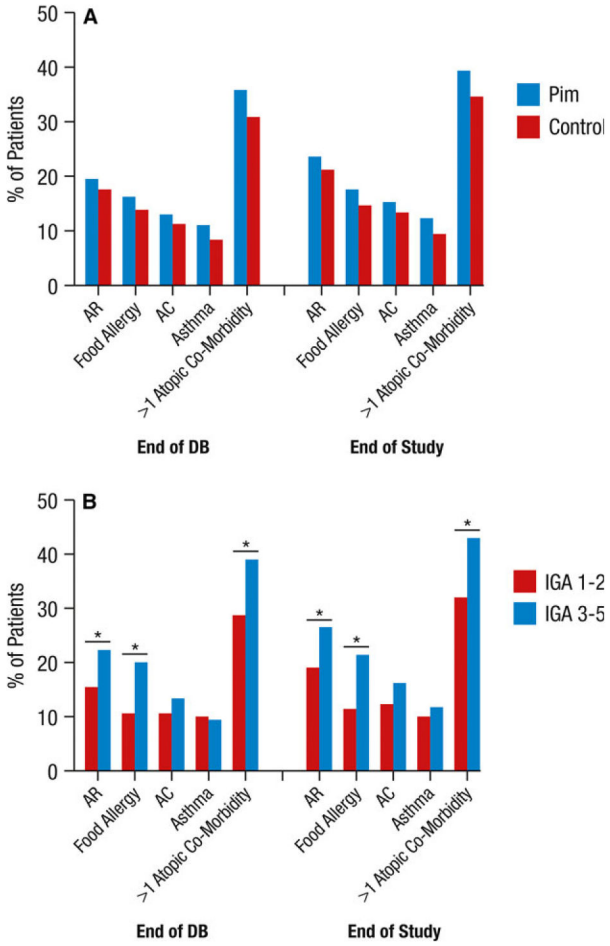

Figure 3.

Development of atopic comorbidities (**A**) in the intent-to-treat (ITT) population and (**B**) according to baseline Investigator Global Assessment (IGA). *p < 0.05. At the end of the double-blind (DB) phase, patients in the pimecrolimus 1% cream (Pim) group continued treatment and those in the control group changed to Pim. AC, allergic conjunctivitis; AR, allergic rhinitis.

TABLE 1

Baseline Demographic and Disease Characteristics

	Safety population			Double-blind phase completers		Double-blind phase noncompleters	
Characteristic	**Pimecrolimus (*n* = 543)**	**Control (*n* = 544)**	**Total (*N* = 1,087)**	**Pimecrolimus (*n* = 291)**	**Control (*n* = 273)**	**Pimecrolimus (*n* = 252)**	**Control (*n* = 271)**
Age, months, mean ± SD	7.1 ± 3.8	7.4 ± 4.1	7.3 ± 3.9	6.8 ± 3.6	7.3 ± 3.9	7.5 ± 3.9	7.5 ± 4.2
Age distribution, months, *n* (%)							
<3	1 (0.2)	2 (0.4)	3 (0.3)	NE	NE	NE	NE
3–6	230 (42.4)	223 (41.0)	453 (41.7)				
6–12	231 (42.5)	220 (40.4)	451 (41.5)				
12–18	81 (14.9)	99 (18.2)	180 (16.6)				
Male, *n* (%)	349 (64.3)	326 (59.9)	675 (62.1)	187 (64.3)	170 (62.3)	162 (64.3)	156 (57.6)
Race, *n* (%)							
Caucasian	375 (69.1)	373 (68.6)	748 (68.8)	223 (76.6)	208 (76.2)	152 (60.3)	165 (60.9)
Black	83 (15.3)	63 (11.6)	146 (13.4)	29 (10.0)	15 (5.5)	54 (21.4)	48 (17.7)
Asian	22 (4.1)	26 (4.8)	48 (4.4)	9 (3.1)	17 (6.2)	13 (5.2)	9 (3.3)
Other	63 (11.6)	82 (15.1)	145 (13.3)	30 (10.3)	33 (12.1)	33 (13.1)	49 (18.1)
Investigator Global Assessment, *n* (%)							
2 (mild)	270 (49.7)	293 (53.9)	563 (51.8)	137 (47.1)	153 (56.0)	133 (52.8)	140 (51.7)
3 (moderate)	235 (43.3)	205 (37.7)	440 (40.5)	133 (45.7)	96 (35.2)	102 (40.5)	109 (40.2)
4 (severe)	35 (6.4)	43 (7.9)	78 (7.2)	20 (6.9)	23 (8.4)	15 (6.0)	20 (7.4)
5 (very severe)	3 (0.6)	3 (0.6)	6 (0.6)	1 (0.3)	1 (0.4)	2 (0.8)	2 (0.7)
Baseline percentage total BSA affected, mean ± SD*	17.6 ± 15.5	17.6 ± 16.0	17.6 ± 15.7	18.6 ± 15.7	16.1 ± 15.4	16.5 ± 15.2	19.1 ± 16.4
Baseline EASI, mean ± SD†	6.4 ± 5.7	6.4 ± 6.2	6.4 ± 6.0	6.8 ± 5.7	5.8 ± 5.4	6.0 ± 5.7	6.9 ± 6.9

*Expressed as a percentage using the area affected component of the Eczema Area and Severity Index (EASI) assessment: (0.2 * head/neck %) + (0.3 * trunk %) + (0.2 * upper limbs %) + (0.3 * lower limbs %).

†Sum of (% of body surface area for body location * score of location * multiplier for body location) for each body location (range 0–72).

NE, not evaluated; SD, standard deviation.

TABLE 2

Development of Atopic Comorbidities

	ITT population													Double-blind phase completers**						
	By end of double-blind phase							By end of study (double-blind and open-label phases)#						By end of double-blind phase††						
	Treatment group				Baseline AD severity			Treatment group				Baseline AD severity			Treatment group				Baseline AD severity		
Comorbidity	Pimecrolimus (*n* = 533)	Control (*n* = 532)	Total (*n* = 1065)	p-Value*	IGA = 1 or 2 (*n* = 552)	IGA = 3–5 (*n* = 513)	p-Value†	Pimecrolimus/ pimecrolimus‡ (*n* = 533)	Control/ pimecrolimus¶ (*n* = 532)	Total (*n* = 1065)	p-Value*	IGA = 1 or 2 (*n* = 552)	IGA = 3–5 (*n* = 513)	p-Value†	Pimecrolimus (*n* = 291)	Control (*n* = 273)	Total (*n* = 564)	p-Value*	IGA= 1 or 2 (*n* = 290)	IGA = 3–5 (*n* = 274)	p-Value†
Age, years, mean ± SD	2.9 ± 1.0	2.8 ± 1.1	2.9 ± 1.1	N/A	–	–	–	3.5 ± 1.5	3.4 ± 1.6	3.4 ± 1.6	N/A	–	–	–	3.7 ± 0.3	3.7 ± 0.3	3.7 ± 0.3	N/A	–	–	–
Allergic rhinitis, *n* (%)	104 (19.5)	93 (17.5)	197 (18.5)	0.54	84 (15.2)	113 (22.0)	0.006	126 (23.6)	113 (21.2)	239 (22.4)	0.55	104 (18.8)	135 (26.3)	0.005	81 (27.8)	65 (23.8)	146 (25.9)	0.32	59 (20.3)	87 (31.8)	0.005
Food allergy, *n* (%)	86 (16.1)	73 (13.7)	159 (14.9)	0.45	58 (10.5)	101 (19.7)	<0.001	92 (17.3)	77 (14.5)	169 (15.9)	0.32	61 (11.1)	108 (21.1)	<0.001	68 (23.4)	56 (20.5)	124 (22.0)	0.53	48 (16.6)	76 (27.7)	0.003
Allergic conjunctivitis, *n* (%)	68 (12.8)	59 (11.1)	127 (11.9)	0.42	59 (10.7)	68 (13.3)	0.25	80 (15.0)	70 (13.2)	150 (14.1)	0.34	67 (12.1)	83 (16.2)	0.08	56 (19.2)	41 (15.0)	97 (17.2)	0.13	42 (14.5)	55 (20.1)	0.16
Asthma, *n* (%)	58 (10.9)	43 (8.1)	101 (9.5)	0.21	53 (9.6)	48 (9.4)	0.84	65 (12.2)	49 (9.2)	114 (10.7)	0.21	55 (10.0)	59 (11.5)	0.46	49 (16.8)	29 (10.6)	78 (13.8)	0.12	44 (15.2)	34 (12.4)	0.24
≥1 atopic comorbidities, *n* (%)	191 (35.8)	164 (30.8)	355 (33.3)	0.12	156 (28.3)	199 (38.8)		210 (39.4)	184 (34.6)	394 (37.0)	0.14	175 (31.7)	219 (42.7)	<0.001	147 (50.5)	116 (42.5)	263 (46.6)	0.14	117 (40.3)	146 (53.3)	0.006

*From a Cochran–Mantel–Haenszel test, adjusted for baseline Investigator Global Assessment (IGA), center, and age.

†p-Value comparing IGA severity subgroups based on logistic regression with effects treatment, sex, and IGA severity subgroup.

‡Patients received pimecrolimus 1% cream during the double-blind and open-label phases.

¶Patients received control cream during the double-blind phase and pimecrolimus 1% cream during the open-label phase.

#Percentage calculated as (number of patients with atopic comorbidity)/(total number of patients in intent-to-treat population [pimecrolimus, *n* = 533; control, *n* = 532; total, *n* = 1,065]*100.

**Patients with atopic conditions could have discontinued the study before completion of the double-blind phase; these patients were not included in this analysis of double-blind completers.

††Percentage calculated as (number of double-blind phase completers with atopic comorbidity)/(total number of double-blind phase completers [pimecrolimus, *n* = 291; control, *n* = 273; total, *n* = 564]*100.

N/A, not applicable; SD, standard deviation.

Pediatr Dermatol. Author manuscript; available in PMC 2017 October 20.

TABLE 3

Analysis of Efficacy Variables

	Week 14					Week 27					Week 158/End of double-blind phase				
Efficacy parameter	**Pimecrolimus (*n* = 533)**	**Control (*n* = 532)**	**Pimecrolimus versus control, difference (95% CI)**	**p–Value**	**p-Value**	**Pimecrolimus (*n* = 533)**	**Control (*n* = 532)**	**Pimecrolimus versus control, difference (95% CI)**	**p-Value**	**p-Value**	**Pimecrolimus (*n* = 533)**	**Control (*n* = 532)**	**Pimecrolimus versus control, difference (95% CI)**	**p-Value**	**p-Value**
Least squares mean															
Proportion of disease-free days, no TCS rescue (Treatment Step 2 or 1)	0.47	0.38	−0.088 (−0.123 to −0.053)	0.001*	0.001†	0.53	0.46	−0.062 (−0.100—0.025)	0.001*	0.009†	0.43	0.43	0.005 (−0.029–0.038)	0.79*	0.86†
Proportion of disease-free days, no study medication or TCS rescue (Treatment Step 1)	0.33	0.28	−0.048 (−0.082 to −0.015)	0.004*	0.005†	0.39	0.35	−0.036 (−0.073–0.000)	0.05*	0.08†	0.36	0.37	−0.006 (−0.040–0.027)	0.71*	0.86†
Longest duration of remission, days	NE	NE	NE			NE	NE	NE			93.35	107.61	−14.26 (−31.28–2.76)	0.10*	0.49†
Change from baseline in total EASI score	−4.64	−3.91	−0.734 (−1.163 to −0.305)	0.001*		−3.96	−3.82	−0.136 (−0.669–0.397)	0.62*		−4.71	−4.56	−0.153 (−0.592–0.287)	0.49*	
Change from baseline in EASI score: head and neck	−1.02	−0.79	−0.235 (−0.381 to −0.089)	0.002*		−0.98	−0.83	−0.148 (−0.297–0.000)	0.05*		−1.20	−0.99	−0.214 (−0.365—0.064)	0.005*	
Change from baseline in TBSA affected	−12.2	−10.5	−1.67 (−2.75 to −0.60)	0.002*		−11.2	−10.5	−0.61 (−1.80–0.58)	0.32*		−13.2	−13.0	−0.20 (−1.18–0.79)	0.69*	
Change from baseline in BSA affected: head and neck	−11.4	−8.3	−3.02 (−4.65 to −1.39)	0.001*		−11.4	−9.4	−1.94 (−3.70—0.17)	0.03*		−13.8	−11.8	−1.98 (−3.71—0.26)	0.02*	
Average pruritus score‡	0.7	0.9	−0.14 (−0.21 to −0.07)	0.001*		0.7	0.7	−0.03 (−0.11–0.05)	0.47*		1.0	1.1	−0.07 (−0.28–0.14)	0.51*	
Average erythema score‡	1.0	1.1	−0.14 (−0.19 to −0.09)	0.001*		1.0	1.0	−0.01 (−0.08–0.05)	0.71*		1.1	1.0	0.06 (−0.13–0.24)	0.54*	
Average number of affected body areas‡	5.0	6.1	−1.18 (−1.65 to −0.71)	0.001*		4.6	4.9	−0.31 (−0.87–0.25)	0.28*		4.9	4.1	0.79 (−0.30–1.88)	0.16*	
IGA of 0 or 1, *n* (%)	298 (55.9)	285 (53.6)		0.77¶		306 (57.4)	301 (56.6)		0.77¶		360 (67.5)	350 (65.8)		0.96¶	

*Based on an analysis of covariance model with treatment, center, sex, baseline age, baseline total Eczema Area and Severity Index (EASI) score, and baseline total body surface area (TBSA) as explanatory variables.

†Based on van Elteren test adjusted for center and sex.

‡Data presented for the first, second, and 13th 3-month intervals.

¶Based on Cochran–Mantel–Haenszel test adjusted for center and sex.

CI, confidence interval; IGA, Investigator Global Assessment; NE, not evaluable; TCS, topical corticosteroid.

TABLE 4

Most Common Adverse Events (≥10% in Total Group in Complete Study) and Serious Adverse Events (Safety Population)

	Double-blind phase, *n* (%)			Complete study, *n* (%)		
Adverse event	**Pimecrolimus**	**Control**	**Total**	**Pimecrolimus/pimecrolimus***	**Control/pimecrolimus†**	**Total**
Patients exposed to drug	543	544	1087	543	544	1087
Patients with a serious adverse event	42 (7.7)	37 (6.8)	79 (7.3)	44 (8.1)	40 (7.4)	84 (7.7)
Patients with an adverse event	486 (89.5)	477 (87.7)	963 (88.6)	488 (89.9)	478 (87.9)	966 (88.9)
Upper respiratory tract infection	288 (53.0)	265 (48.7)	553 (50.9)	300 (55.2)	277 (50.9)	577 (53.1)
Otitis media	264 (48.6)	260 (47.8)	524 (48.2)	274 (50.5)	275 (50.6)	549 (50.5)
Cough	187 (34.4)	174 (32.0)	361 (33.2)	202 (37.2)	191 (35.1)	393 (36.2)
Nasopharyngitis	186 (34.3)	175 (32.2)	361 (33.2)	201 (37.0)	182 (33.5)	383 (35.2)
Allergic rhinitis	122 (22.5)	107 (19.7)	229 (21.1)	148 (27.3)	134 (24.6)	282 (25.9)
Teething	134 (24.7)	135 (24.8)	269 (24.7)	138 (25.4)	141 (25.9)	279 (25.7)
Food allergy‡	140 (25.8)	118 (21.7)	258 (23.7)	149 (27.4)	126 (23.2)	275 (25.3)
Pyrexia	123 (22.7)	123 (22.6)	246 (22.6)	131 (24.1)	130 (23.9)	261 (24.0)
Wheezing	102 (18.8)	89 (16.4)	191 (17.6)	118 (21.7)	100 (18.4)	218 (20.1)
Allergic conjunctivitis	76 (14.0)	63 (11.6)	139 (12.8)	92 (16.9)	81 (14.9)	173 (15.9)
Viral gastroenteritis	76 (14.0)	69 (12.7)	145 (13.3)	85 (15.7)	80 (14.7)	165 (15.2)
Sinusitis	75 (13.8)	61 (11.2)	136 (12.5)	79 (14.5)	69 (12.7)	148 (13.6)
Asthma	64 (11.8)	53 (9.7)	117 (10.8)	75 (13.8)	62 (11.4)	137 (12.6)
Rhinorrhea	68 (12.5)	63 (11.6)	131 (12.1)	67 (12.3)	65 (11.9)	132 (12.1)
Streptococcal pharyngitis	35 (6.4)	55 (10.1)	90 (8.3)	45 (8.3)	71 (13.1)	116 (10.7)
Gastroenteritis	55 (10.1)	50 (9.2)	105 (9.7)	59 (10.9)	51 (9.4)	110 (10.1)

*Patients received pimecrolimus 1% cream during the double-blind and open-label phases.

†Patients received control cream during the double-blind phase and pimecrolimus 1% cream during the open-label phase.

‡Includes reactions reported to all foods.