

# Improvement in Pruritus in Children With Atopic Dermatitis Using Pimecrolimus Cream 1%

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*The objective of this study was to assess time to onset of pruritus improvement in a pediatric population treated with pimecrolimus cream 1%. This 8-day, double-blinded, vehicle-controlled study randomized 174 children and adolescents (aged 2–17 years) with mild to moderate atopic dermatitis (AD) and moderate to severe pruritus to twice-daily applications of pimecrolimus cream 1% or vehicle. There were no significant between-group differences in demographics or baseline disease characteristics. Pruritus was assessed by subjects using a 4-point pruritus severity scale (0–3). The primary efficacy variable was time to a 1 point or more improvement in pruritus score from baseline. The 2 treatment groups were compared using log-rank testing of the time-to-event data. In the per-protocol (PP) population, median times to a 1 point or more improvement in pruritus score were 48 and 72 hours for pimecrolimus and vehicle groups, respectively (P=.038). From day 3 onward, significantly more subjects (P=.023) in the pimecrolimus group versus the vehicle group reported complete pruritus resolution. Pimecrolimus cream 1% improved pruritus within 48 hours in children and adolescents with mild to moderate AD and achieved complete resolution of*

*pruritus in a significantly greater number of subjects in the pimecrolimus group versus the vehicle group by the end of the 7-day treatment period (P=.008).*

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**I**ntense pruritus is a primary complaint in individuals with atopic dermatitis (AD). The threshold for pruritus is lowered in individuals with AD, and stimulation leads to a longer duration of pruritus compared with healthy individuals.<sup>1,4</sup> After itching begins, scratching follows, which worsens and extends the skin inflammation. This process is commonly referred to as the circular itch-scratch cycle of AD.<sup>1,5</sup>

Beyond the physical discomfort, intense itching also psychologically affects patients and families by causing sleep deprivation, which can negatively affect work/school performance and interpersonal relationships and can cause depression.<sup>6,7</sup> Consequently, for many physicians, patients, and caregivers, improvement or resolution of itch is the key determinant used to assess the efficacy of treatments for AD.

Pimecrolimus cream 1%, a nonsteroid topical calcineurin inhibitor, decreases cytokine production and T-cell activation by blocking the calcineurin transcription pathway in T cells and preventing mast cell degranulation.<sup>8</sup> The drug is effective in the treatment of both skin inflammation and pruritus associated with AD in infants, children, and adults.<sup>9-12</sup> The prescribing information for topical calcineurin inhibitors, including pimecrolimus, recently has been revised to include a boxed warning and medication guide. These changes inform patients and healthcare providers that, although a causal relationship has not been established, rare cases of malignancy, including skin and lymphoma, have been reported in patients treated with topical calcineurin inhibitors, including pimecrolimus.<sup>13</sup>

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In large clinical studies of pimecrolimus, 118 of 267 children (44%) and 86 of 123 caregivers of infants (70%) reported absent or mild pruritus at the first postbaseline visit following 7 days of treatment with pimecrolimus.<sup>9,14</sup> These data suggest that, for most subjects, pruritus relief began within the first few days of treatment. In one study of adults with moderate to severe AD, pimecrolimus was shown to improve pruritus within the first 2 days of treatment, but pruritus was not the main focus of the study and pruritus has never been evaluated before day 8 of therapy in the pediatric population.<sup>12</sup> The present study is the first study to specifically evaluate the time to onset of pruritus improvement as the primary outcome measure in children with mild to moderate AD after beginning topical pimecrolimus treatment.

## Methods

**Subjects**—Children and adolescents (aged 2–17 years) diagnosed with AD using criteria established by Williams et al<sup>15</sup> were enrolled at 15 US centers. Subjects had mild to moderate AD (investigator global assessment [IGA] score of 2 or 3) involving at least 5% total body surface area with moderate to severe pruritus (baseline pruritus score of 2 or 3). Subjects who were immunocompromised, had a concurrent skin disease that could interfere with evaluations, had AD triggered by a known unavoidable allergen or irritant, or had an active viral or bacterial infection were excluded from the study.

**Study Design**—This study was approved by a medical ethics committee, and the legal guardian of each subject signed a written informed consent agreement. All subjects or their caregivers were required to apply a bland emollient starting at least 3 days prior to randomization and continuing throughout the 7-day treatment period. No topical and systemic agents known or thought to have efficacy in treating AD or its associated pruritus, including sedating antihistamines, were permitted during the study. Washout periods were as follows: topical medications, except emollients, 1 week; systemic medications with a known antipruritic effect, 2 weeks; systemic AD therapies, 4 weeks; topical tacrolimus ointment and pimecrolimus cream, 2 weeks; and systemic antibiotics, 1 week.

Subjects were randomized in a 1:1 ratio using a double-blinded randomization scheme to apply either pimecrolimus cream 1% or the corresponding vehicle of identical appearance, consistency, and odor twice daily to all affected areas for 7 consecutive days. The overall study design is shown in Figure 1.

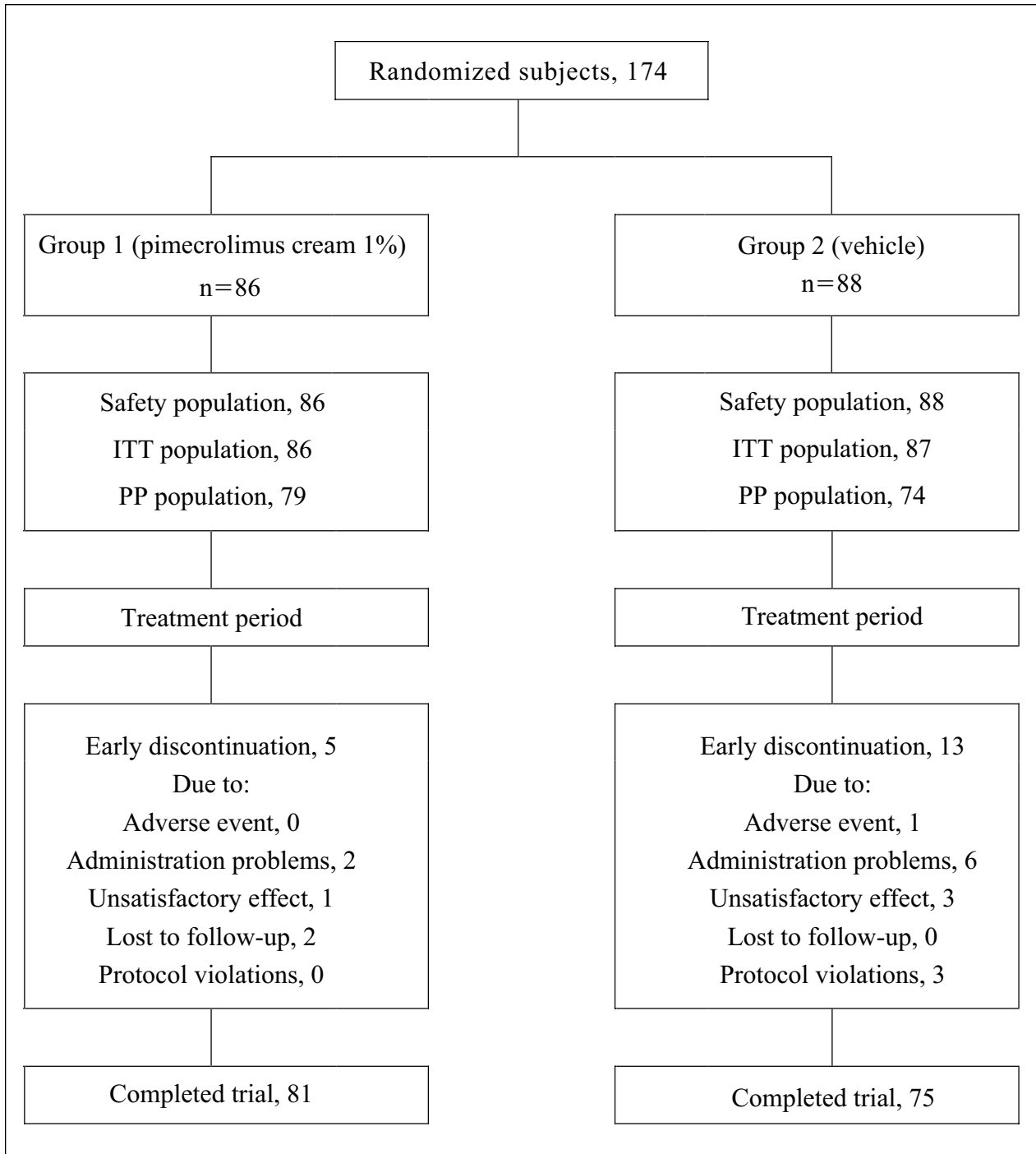
**Assessments**—The safety population included all randomized subjects who took 1 or more doses of study drug. The intent-to-treat (ITT) population included all randomized subjects who took at least 1 dose of study drug and from whom at least 1 postbaseline efficacy measurement was obtained. The per-protocol (PP) population included all ITT subjects with a baseline pruritus score (taken via a telephone interactive voice response system) of 2 (moderate) or 3 (severe). The PP analysis was considered necessary to exclude subjects whose pruritus substantially improved to either mild or absent in the 24 hours between screening and baseline, before treatment with study drug was initiated.

The primary efficacy variable was time to a 1 point or more pruritus score improvement from baseline. The pruritus severity score consisted of a 4-point scale used to evaluate the intensity of itching and scratching over the preceding 24-hour period (0 [absent]=no pruritus; 1 [mild]=occasional slight itching and scratching; 2 [moderate]=constant or intermittent itching and scratching that is not disturbing sleep; 3 [severe]=bothersome itching and scratching that is disturbing sleep). Pruritus severity scores were recorded by subjects or their caregivers via a telephone interactive voice response system between 7:00 AM and noon each day during the treatment period. If no pruritus score was recorded by noon, subjects or their caregivers were contacted by the investigator as a reminder. Additional ad hoc analyses included the daily percentages of subjects in each treatment group who achieved a 2 point or more improvement over the baseline pruritus score and who achieved a pruritus score of 0 (absent). All pruritus outcomes, including the primary efficacy variable, were reported for both the ITT and PP populations.

A secondary efficacy outcome was the percentage of subjects at study completion with a 1 point or more IGA score improvement from baseline. The IGA is a 6-point scale (0 [clear]=no inflammatory signs of AD; 1 [almost clear]=just perceptible erythema, infiltration, or papulation; 2 [mild disease]=mild erythema, infiltration, or papulation; 3 [moderate disease]=moderate erythema, infiltration, or papulation; 4 [severe disease]=severe erythema, infiltration, or papulation; 5 [very severe disease]=severe erythema, infiltration, or papulation, with oozing and crusting). The IGA efficacy outcome was reported for the ITT population only.

Safety was assessed by monitoring and recording all emergent adverse events (AEs) throughout the study.

**Statistical Analysis**—Demographic and background variables were analyzed using a 2-sample



**Figure 1.** Flow diagram of subject treatment. Subjects were randomized in a 1:1 ratio to receive pimecrolimus cream 1% or vehicle twice daily for 7 consecutive days. ITT indicates intent to treat; PP, per protocol.

*t* test or a  $\chi^2$  test. The primary efficacy variable and other time-to-event variables were analyzed using the Kaplan-Meier method, and the 2 treatments were compared using the log-rank test. The binary efficacy variables were analyzed using a Cochran-Mantel-Haenszel test, adjusting for center.

The sample size was based on the primary efficacy variable. Using existing data and clinical

judgment, it was expected that after 7 days of treatment, 70% of subjects in the pimecrolimus group would demonstrate pruritus improvement versus 40% in the vehicle group. With a 1:1 allocation ratio, a 2-sided log-rank test, a significance level of .05, and a nonevaluability rate of 0.10, approximately 170 subjects (85 subjects in each treatment group) provided 95% power.<sup>16</sup>

## Results

**Subject Demographics and Disposition**—A total of 174 children and adolescents were randomized to treatment with pimecrolimus cream 1% (n=86) or vehicle (n=88). One subject in the pimecrolimus group dropped out before the first application of study drug. Both groups were well matched in demographic and baseline disease characteristics (Table 1). Mean ages were 6.5 years in the pimecrolimus group and 7.4 years in the vehicle group. At baseline, approximately one third of each group had mild AD (baseline IGA=2) and approximately two thirds had moderate AD (baseline IGA=3)(Table 2). Mean baseline pruritus scores were similar for both treatment groups (2.2 for pimecrolimus and 2.1 for vehicle,  $P=.470$ ) and represented moderate pruritus severity.

A higher percentage of subjects in the vehicle group (15%) discontinued prior to study completion than subjects in the pimecrolimus group (6%). A similar percentage of both groups discontinued early for all reasons (ie, adverse event, unsatisfactory effect, lost to follow-up) except protocol violations

(0% of pimecrolimus group, 3% of vehicle group) and administrative problems (2% of pimecrolimus group, 7% of vehicle group)(Figure 1).

The safety, ITT, and PP populations comprised 174, 173, and 153 subjects, respectively. The PP population excluded 20 subjects from the ITT population (7 subjects in the pimecrolimus group and 13 subjects in the vehicle group) whose pruritus score improved to either 1 (mild) or 0 (absent) in the 24 hours between screening and baseline visits, before the first application of study drug.

**Efficacy**—Subjects treated with pimecrolimus reported faster improvement of their pruritus. A higher percentage of this group achieved greater levels of pruritus improvement, including total resolution of pruritus versus subjects in the vehicle group. In the ITT population, the median time from initiation of treatment to a 1 point or more improvement in pruritus score was 48 hours for the pimecrolimus group versus 72 hours for the vehicle group, a difference that approached significance ( $P=.084$ ). In the PP population, in which only subjects with

Table 1.

### Demographic and Baseline Characteristics of Subjects by Treatment Group\*

Characteristic	ITT Population <sup>†</sup>			PP Population <sup>‡</sup>		
	Pimecrolimus Cream 1% (n=86)	Vehicle (n=88)	Total (N=173)	Pimecrolimus Cream 1% (n=79)	Vehicle (n=74)	Total (N=153)
Age, y						
Mean±SD	6.5±4.1	7.4±4.2		6.5±4.1	7.8±4.2	7.1±4.2
Range	2–17	2–17	2–17	2–17	2–17	2–17
P value <sup>§</sup>			.131			.049
IGA score <sup>  </sup> , mean	2.7	2.6		2.7	2.7	
P value <sup>§</sup>			.453			.786
Pruritus severity score, <sup>¶</sup> mean	2.2	2.1		2.3	2.3	
P value <sup>§</sup>			.470			.774

\*ITT indicates intent to treat; PP, per protocol; IGA, investigator global assessment.

<sup>†</sup>All randomized subjects who applied  $\geq 1$  dose of study drug and from whom  $\geq 1$  postbaseline efficacy measurement was obtained.

<sup>‡</sup>All ITT subjects with baseline pruritus score of 2 (moderate) or 3 (severe).

<sup>§</sup>Based on a 2-tailed *t* test.

<sup>||</sup>IGA score (0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease, 5=very severe disease).

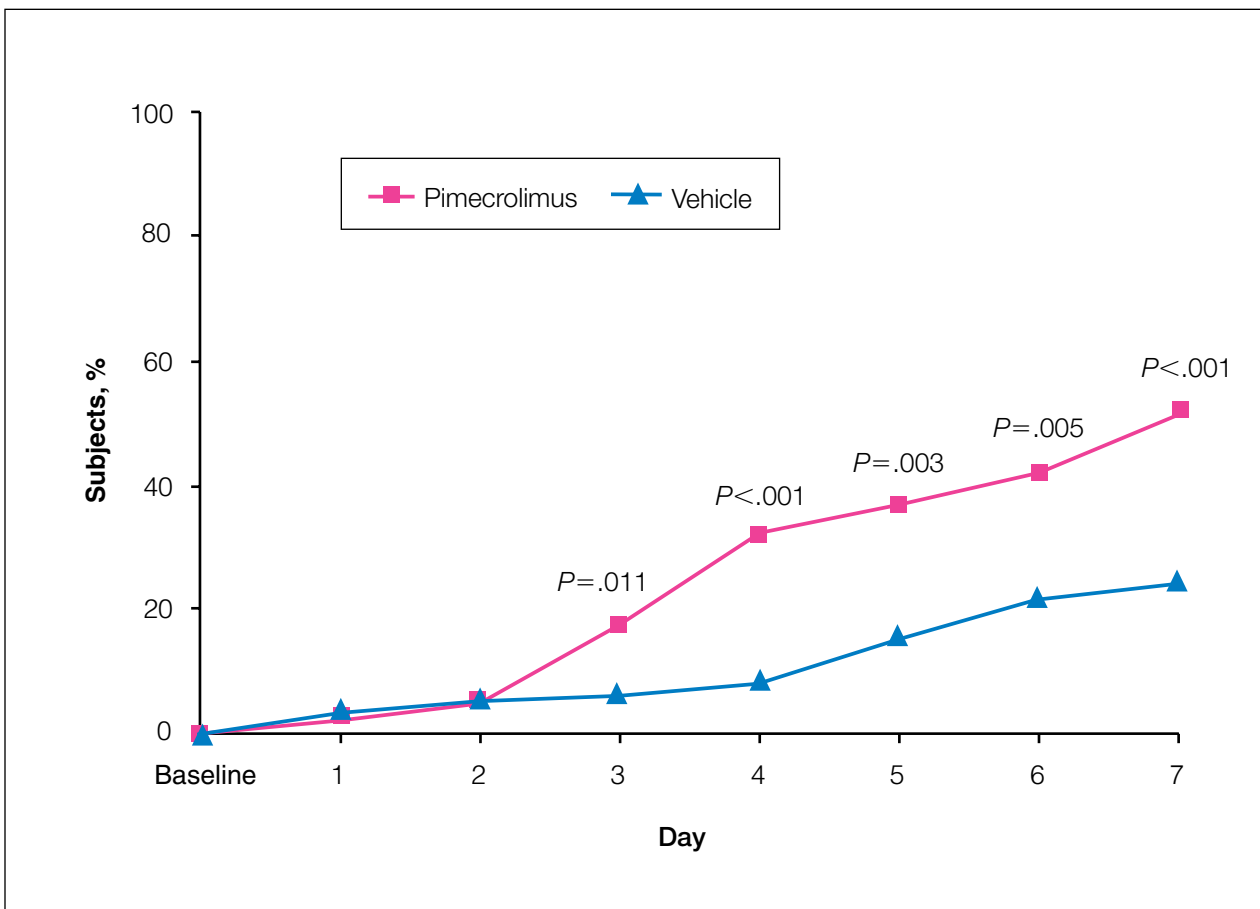
<sup>¶</sup>Pruritus severity score (0=absent, 1=mild, 2=moderate, 3=severe).

Table 2.

**Baseline IGA Score Distribution\***

IGA Score	Pimecrolimus Cream 1%, n (%) n=86	Vehicle, n (%) n=88	P value <sup>†</sup>
0 (clear)	0 (0)	0 (0)	.450
1 (almost clear)	0 (0)	0 (0)	
2 (mild disease)	26 (30)	31 (36)	
3 (moderate disease)	60 (70)	56 (64)	
4 (severe disease)	0 (0)	0 (0)	
5 (very severe disease)	0 (0)	0 (0)	

\*IGA indicates investigator global assessment.  
<sup>†</sup>P value based on the  $\chi^2$  test.



**Figure 2.** Percentage of subjects (per-protocol population) with 2 point or more improvement vs baseline in pruritus score. P values were derived from  $\chi^2$  tests performed on Kaplan-Meier data. Between-group significance was demonstrated on day 3 and was sustained until the end of the treatment period.

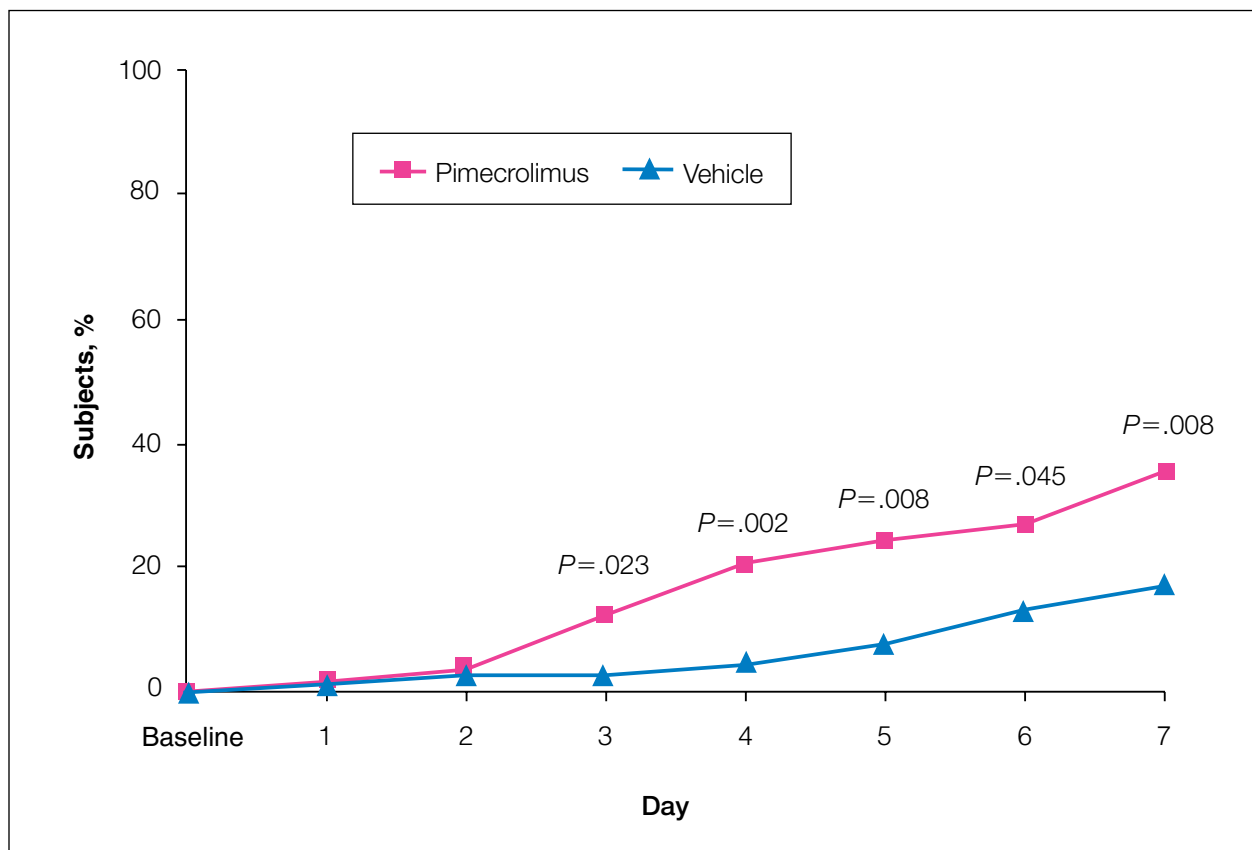
moderate or severe pruritus at baseline were evaluated, median times to improvement reported were the same as the ITT group; however, the difference was significant ( $P=.038$ ).

In 20 subjects, the pruritus score changed from 2 or 3 to 0 or 1 between screening and baseline, suggesting that 1-point changes are not uncommon. Therefore, sensitivity testing was conducted using a more stringent 2 point or more pruritus score improvement. Significantly more of the pimecrolimus group achieved at least a 2-point improvement in pruritus beginning on day 3 of treatment (19% of the pimecrolimus group vs 5.4% of the vehicle group, PP population,  $P=.011$ ). After 7 days of treatment, these proportions increased to 51.9% of the pimecrolimus group and 25.7% of the vehicle group ( $P<.001$ )(Figure 2).

Significantly more of the pimecrolimus group (13%) than the vehicle group (3%) reported complete pruritus resolution beginning on day 3 of treatment (PP population,  $P=.023$ ). By day 7, these proportions had increased to 37% for the pimecrolimus group and 18% for the vehicle group (PP population,  $P=.008$ )(Figure 3).

A significant between-group difference also was observed for improvement of the inflammatory signs of AD. At day 7, a greater proportion of the pimecrolimus group (69%) than the vehicle group (53%) had a 1 point or more improvement from baseline IGA score ( $P=.031$ ).

**Safety**—In general, AEs were of mild to moderate severity and were reported in low and similar incidences for both treatment groups. For most individual AEs, the incidence was no more than 1 subject in either treatment group. AEs that were reported by more than 1 subject in either group were impetigo, reported by 2 subjects (2.3%) in the vehicle group and 1 subject (1.2%) in the pimecrolimus group, and headache, reported by 2 subjects (2.3%) in the pimecrolimus group and no subjects in the vehicle group. One subject in the vehicle group discontinued early because of impetigo that was suspected to be related to study medication; no subjects in the pimecrolimus group discontinued secondary to an AE. No serious AEs were reported in either group. Both pimecrolimus and its corresponding vehicle were well-tolerated, with only 1 report of



**Figure 3.** Percentage of subjects (per-protocol population) with complete pruritus resolution (pruritus score=0 [absent]).  $P$  values were derived from  $\chi^2$  tests performed on Kaplan-Meier data. Between-group significance was demonstrated at day 3 and was sustained until the end of the treatment period.

application site burning in the vehicle group and no reports in the pimecrolimus group.

### Comment

Pruritus is one of the most bothersome symptoms for patients with AD. When a child has intense pruritus, negative behavior, poor school performance, and sleep deprivation for the child and other family members can result. In addition, pruritus is the driver of the itch-scratch cycle that initiates and sustains exacerbations of AD. Therefore, it is useful for both physicians and their patients to be aware of the time frame when a treatment can be expected to begin improving the pruritus.

In our study, pimecrolimus cream 1% effected a rapid and notable pruritus improvement. Within 48 hours of starting treatment, pruritus improvement was observed in the pimecrolimus group, and complete pruritus resolution began the following day in significantly more pimecrolimus-treated subjects than in the vehicle group ( $P=.023$ ). This favorable effect became more pronounced throughout the remainder of the trial. Raising the stringency from a modest 1-point to 2-point improvement in pruritus, and even to complete pruritus resolution, only made the separation between pimecrolimus and vehicle more pronounced. These results confirm trends and findings from previous trials.<sup>9-12</sup>

The antipruritic activity of pimecrolimus cream complements well its proven anti-inflammatory activity in AD.<sup>9-12,17</sup> It is not surprising that pimecrolimus improved skin inflammation while improving pruritus, an effect that has been previously observed.<sup>9-12</sup> This observation supports the conjecture that skin inflammation and pruritus in AD are mediated by similar immune mechanisms. Certain inflammatory cytokines, such as interleukin 2, are well-known as potent mediators of itch; and cyclosporin A, an interleukin 2 inhibitor, has potent antipruritic effects in AD.<sup>18-21</sup> Pimecrolimus targets T cells, the primary effector cells of AD,<sup>8,22</sup> and probably reduces and/or resolves AD-associated pruritus, primarily through its inhibitory effects on T-cell inflammatory cytokine production and release. This study suggests that for most children with mild to moderate AD, additional specific antipruritic therapies such as sedating antihistamines may not be required.

### Conclusion

Pimecrolimus cream 1% improved pruritus within 48 hours and began to completely resolve pruritus by the following day in children and adolescents with mild to moderate AD. By breaking the itch-scratch

cycle early, pimecrolimus may facilitate faster control of this skin condition.

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