Steroid-Free Over-the-Counter Eczema Skin Care Formulations Reduce Risk of Flare, Prolong Time to Flare, and Reduce Eczema Symptoms in Pediatric Subjects With Atopic Dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic skin condition associated with decreased barrier function resulting in periodic flare-ups of erythematous and pruritic lesions. Guidelines recommend daily treatment of atopic skin with emollient moisturizers for prevention of flares and maintenance of the flare-free state. This study evaluated the efficacy of 2 steroid-free, nonprescription eczema skin care formulations for reducing the risk of flare and relieving symptoms in infants and children with AD: Body Cream for the daily maintenance treatment of atopic skin and Flare Treatment for the treatment of atopic flares.

Methods: After a 2-week washout period, subjects (N=45; mean age 3.5 years) were randomized to cleanser plus daily moisturizing with Body Cream (moisturizer group) or cleanser only (control group) for 6 months or until flare. Subjects experiencing flare received Flare Treatment for 4 weeks.

Results: The incidence of flare was significantly lower in the moisturizer group compared with the control group (21% vs 65%; *P*=.006), while the median time to flare was shorter in the control group (28 vs >180 days). Risk of flare was reduced by 44.1% after 6 months of Body Cream application. Flare Treatment reduced overall eczema symptom severity at week 2 and week 4; 78.9% of flares had improved or cleared at week 4.

Conclusions: Body Cream reduced the incidence of flare and the time to flare, reinforcing guidelines that daily emollient therapy should be an integral part of the maintenance treatment plan for the prevention of disease flares. Body Cream and Flare Treatment are effective over-the-counter steroid-free options for management of AD in children.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic skin condition affecting 1% to 3% of adults and 15% to 30% of children.[1,2] It is characterized by dry, irritated skin with periodic flare-ups of lesions involving erythema, edema, and pruritus.[2-4]

The contemporary hypothesis of the etiology of AD consists of 2 opposing theories: the outside-in theory (barrier theory) and the inside-out theory (immune theory). The outside-in theory contends that a defective skin barrier function allows infection and transepidermal water loss (TEWL), leads to pro-inflammatory responses, provokes itching, and is exacerbated by subsequent scratching behaviors. The inside-out theory proposes that the barrier dysfunction results from an increased expression of proinflammatory signaling molecules, which then allows TEWL and infection to occur.[5,6]

Regardless of the underlying pathogenesis, both the barrier theory and immune theory highlight the central role the skin barrier plays in flare onset. Therefore, if the skin barrier function in AD patients can be maintained, there will be an associated reduction not only in the number of flares and degree of severity an individual experiences, but also in the frequency of eczematous flares an individual experiences over a given amount of time.

European and US guidelines recommend daily application of emollient moisturizers for the prevention and treatment of symptoms of AD.[4,7,8] Moisturizers should be an integral part of the maintenance treatment plan for the prevention of disease flares.[9] Moisturizers help treat xerosis and counteract TEWL caused by a defective skin barrier, and in controlled clinical trials have been demonstrated to reduce symptoms of AD, particularly pruritus, erythema, fissuring, and lichenification.[7] Topical corticosteroids are the primary prescription product used to control flare-ups of AD, providing anti-inflammatory benefits,[4,7,8,10] and are usually prescribed when good skin care and daily moisturizing have not been sufficient to heal lesions.[7] However, topical steroids do

not address barrier dysfunction and their long-term use is not recommended, particularly in children, due to the risk of cutaneous side effects, rebound flare-ups, suppression of growth rate, and reduced bone density.[4,6,8] Moreover, studies have shown that parents are reluctant to use steroids, with more than 50% delaying steroid treatment until flares have progressed to more severe presentations.[11,12] Hence, there is a need for steroid-free nonprescription therapies for the treatment of pediatric AD.

Two nonprescription products have been specifically developed for the care and treatment of eczematous skin—one developed as a daily maintenance moisturizer (Eucerin® Eczema Relief Body Crème, Beiersdorf, Wilton, CT) and the other for the acute treatment of AD lesions (Eucerin® Eczema Relief Flare Treatment). These over-the-counter (OTC) formulations are specifically designed to help restore optimal acidic skin pH, restore and maintain barrier function, and provide relief for pruritus and irritation due to eczema. Both formulations contain 1% colloidal oatmeal, a skin protectant used as a bath additive for centuries to alleviate itch[13]; licochalcone A, a retrochalcone from the root of *Glycyrrhiza inflata* that visibly helps relieve irritated skin[14]; and ceramide 3, an epidermal barrier lipid. The Flare Treatment product is formulated with a higher concentration of ceramides than the Body Cream to help promote barrier repair of lesional skin, and also contains menthoxypropanediol—a novel cooling agent that helps soothe itch.[15] Both formulations have previously demonstrated efficacy and tolerability in trials involving adults[16] and infants and children.[17] In these studies, the Body Cream moisturizer effectively moisturized skin and improved and maintained barrier function, while the acute Flare Treatment reduced the severity of acute AD symptoms, significantly improved scores of itch intensity and duration, and reduced the impact of itch on life activities as measured by Elman's 5-D itch questionnaire.[16,17]

To further evaluate the role of these OTC formulations in the management of atopic disease, a randomized, controlled, 6-month prospective study was conducted to assess the efficacy of daily use of the Body Cream moisturizer in maintaining and prolonging the flare-free state of asymptomatic infants and children with AD relative to a control group, and to evaluate the efficacy of the acute Flare Treatment product to manage AD symptoms in subjects who experienced flare.

METHODS

Subjects

Infants and children from ages 3 months through 12 years were eligible for enrollment. Subjects were required to have a history of AD, as confirmed by a board-certified dermatologist, and meet the Hanifin and Rajka AD criteria.[3] Subjects were excluded if they had active lesions/eczema flares at the time of enrollment. Parents/legal guardians of prospective subjects read and signed an Institutional Review Board-approved informed consent form prior to study enrollment.

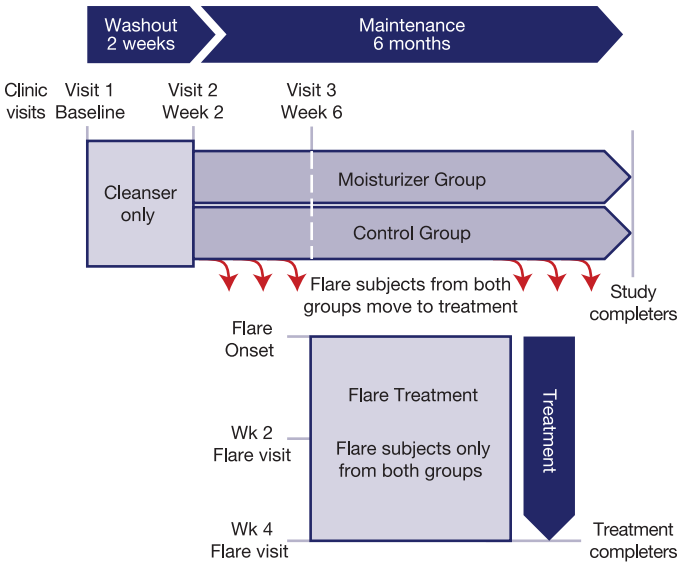
Products

Three products developed specifically by Beiersdorf Inc. (Wilton, CT) for the skin care and treatment of AD were used in this study: (1) a mild daily cleansing body wash formulated with a mild surfactant system (decyl glucoside, sodium myreth sulfate) and panthenol (cleanser) to provide gentle cleansing for atopic skin without drying; (2) a daily moisturizing body cream (Eucerin® Eczema Relief Body Crème, referred to hereafter as "Body Cream"); and (3) an acute therapy for active AD lesions (Eucerin® Eczema Relief Instant Therapy, referred to hereafter as "Flare Treatment").

Study Design

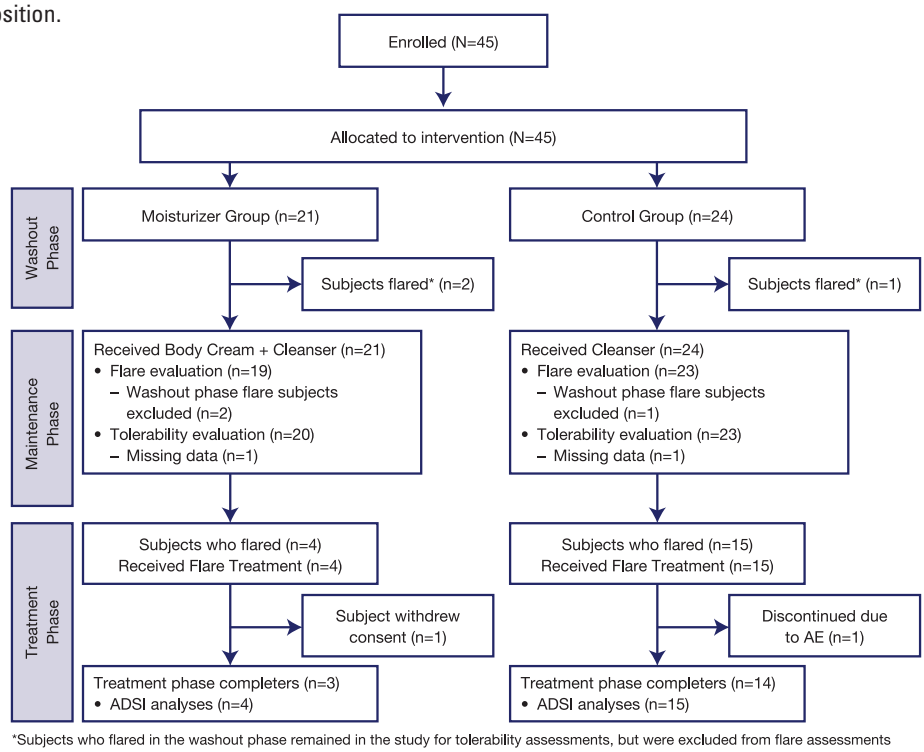
This single-center, randomized trial consisted of a washout phase (2 weeks), a maintenance phase (6 months), and a treatment phase (4 weeks) (Figure 1). Scheduled clinic evaluations took place at the baseline of the washout phase (visit 1), the baseline of the maintenance phase/conclusion of the washout phase (visit 2), and 4 weeks into the maintenance phase (visit 3). If a flare occurred, subjects entered the treatment phase and were assessed at onset, week 2, and week 4.

FIGURE 1. Study design. The study was conducted in 3 phases. A 2-week washout phase for all subjects, in which only the supplied cleanser was used for bathing; a maintenance phase, in which subjects received daily Body Cream + cleanser (moisturizer group) or cleanser only (control group) for 6 months. Subjects who flared entered the 4-week treatment phase, in which flares were assessed at onset and at week 2 and week 4 of treatment.



Parents/guardians were instructed not to use any topical moisturizing products on their children 2 days prior to visit 1, or any eczema treatment products for at least 5 days prior to the visit. At enrollment, subjects were randomly assigned to the moisturizer group (n=22) or the control group (n=23), and parents/guardians completed an eczema history questionnaire. All participants completed a 2-week washout phase in which a standardized

FIGURE 2. Subject disposition.



*Subjects who flared in the washout phase remained in the study for tolerability assessments, but were excluded from flare assessments

gentle cleanser was used for all bathing, and bathing time was limited to less than 8 minutes and rinsing with lukewarm water. No other skin care products were permitted.

For the maintenance phase, the moisturizer group used Body Cream on the entire body at least once per day in addition to the cleanser, while the control group continued with cleanser only (no moisturizer) for 6 months, or until a flare occurred.

Subjects who developed a flare entered the treatment phase. Flare Treatment was applied to the affected area each morning and evening, or more often as necessary, for 4 weeks. After 4 weeks of Flare Treatment, subjects ceased participation in the study.

Assessments

Moisturizer and control groups were compared for the number of subjects who flared in each group and for the time to flare in each group (including mean, median, minimum, and maximum days to flare). Flares were assessed at all treatment phase visits by clinical grading of eczema symptoms of lesions, including erythema, pruritus, exudation, excoriation, and lichenification (0=none, 1=mild, 2=moderate, 3=severe), and by the Atopic Dermatitis Severity Index (ADSI, 0-15 scale), the sum of the component eczema symptom scores. At weeks 2 and 4 of treatment, the degree of improvement was graded by the investigator according the following scale: 1=markedly worse, 2=moderately worse, 3=no change, 4=moderate improvement, 5=marked improvement, 6=clear/almost clear.

Global tolerability was graded by the investigator from 1=excellent to 4=poor at visit 2 (end of washout phase) and visit 3 (week 4 of maintenance phase). For subjects who flared, global tolerability of flare treatment was assessed at weeks 2 and 4 of the treatment phase.

Statistics

Differences between groups in number and percentage of subjects who flared were analyzed using the Fisher exact test. Significant difference in time to flare between groups was calculated using the log-rank test. Change in ADSI scores between baseline, week 2, and week 4 of the treatment phase and between groups were tested for significance using the Wilcoxon signed rank test.

Global tolerability data analysis compared favorable (excellent and good) vs unfavorable (fair and poor) tolerability using a binomial (sign) test (null hypothesis). All statistical tests were 2-sided at a significance level α of .05 and were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of the 45 subjects who were enrolled at baseline, 43 completed the study. Two subjects who flared discontinued during the treatment phase (Figure 2). Subjects ranged in age from 7 months to 11 years 5 months (mean, 3.5 years) (Table 1).

TABLE 1.

Baseline Demographic Characteristics of the Intent-to-Treat Population

	Washout Phase	Maintenance Phase	
	All Subjects	Moisturizer Group	Control Group
N[a]	45	21	24
Age, months			
Mean (SD)	42.6 (37.8)	37.8 (31.3)	46.8 (42.8)
Median (min, max)	22.0 (7, 137)	22.0 (7, 109)	22.5 (9, 137)
Sex, n (%)			
Female	21 (46.7)	8 (38.1)	13 (54.2)
Male	24 (53.3)	13 (61.9)	11 (45.8)
Ethnicity/Race, n (%)			
Native American/Alaska Native	1 (2.2)	0 (0.0)	1 (4.2)
Black/African American	7 (15.6)	3 (14.3)	4 (16.7)
Hispanic/Latino	6 (13.3)	4 (19.0)	2 (8.3)
White	20 (44.4)	7 (33.3)	13 (54.2)
Mixed	11 (24.4)	7 (33.3)	4 (16.7)
Age Group, n (%)			
3-12 months	3 (6.7)	1 (4.8)	2 (8.3)
> 12-24 months	21 (46.7)	10 (47.6)	11 (45.8)
> 24 months-12 years	21 (46.7)	10 (47.6)	11 (45.8)

[a]Includes 2 discontinued subjects in the intent-to-treat population.

Washout Phase Baseline Questionnaire

The eczema history questionnaire completed at baseline showed that 78% of subjects had flared 3 to 4 times in the previous 12 months, while 18% had flared 1 to 2 times during this time period. When asked about the treatment of the last flare their child had experienced, the majority of parents/guardians responded that they managed their child's treatment on their own (69%), while the remainder visited a pediatrician (27%), dermatologist (2%), or a general practitioner (2%). The most common treatments used, as reported by parents/guardians, were moisturizer (60%) or 1% non-prescription hydrocortisone (40%) (Figure 3A). Overall, 44% of parents were not concerned about using prescription products to treat their child's eczema, while 40% did not use prescription products to treat their child's eczema (Figure 3B).

"Due to the chronic, relapsing nature of AD, it is important to adopt skin care practices that can help minimize flare incidence and severity."

Maintenance Phase Assessments

A total of 19 subjects were confirmed to have eczema flares during the maintenance phase. Only 4 of 19 subjects (21%) flared in the moisturizer group, vs 15 of 23 (65%) in the control group, a statistically significant difference (P=.006; Figure 4). In addition, control group subjects flared earlier (mean 27.8 days) than the moisturizer group subjects (55 days) (Table 2). Considering all subjects who completed the study (n=43), the median time to flare was 28 days for the control group and more than 180 days for the moisturizer group (Table 2).

The differences between groups in time to flare and the number of subjects who experienced flare were statistically significant (P<.05) (Figure 5). At the end of the 6-month maintenance phase, 78.9% of subjects in the moisturizer group remained flare-free, compared with 34.8% of the control group, indicating a 44.1% reduction in risk of flare after 6 months of daily application of Body Cream. The overall hazard ratio for risk of flare in the maintenance phase was 4.74 (95% CI, 1.57-14.38).

Treatment Phase Flare Assessments

The 19 subjects who flared during the maintenance phase entered the 4-week treatment phase. Application of Flare Treatment

FIGURE 3. Subjects' eczema history. Parents/guardians completed a questionnaire on the history of their children's eczema at baseline. **A)** Treatment of each subject's last flare. **B)** Parents were asked if they were concerned about frequent use of OTC or prescription products when treating their child's eczema. Parents were allowed to select all applicable statements, therefore responses may total >100%. OTC, over-the-counter.

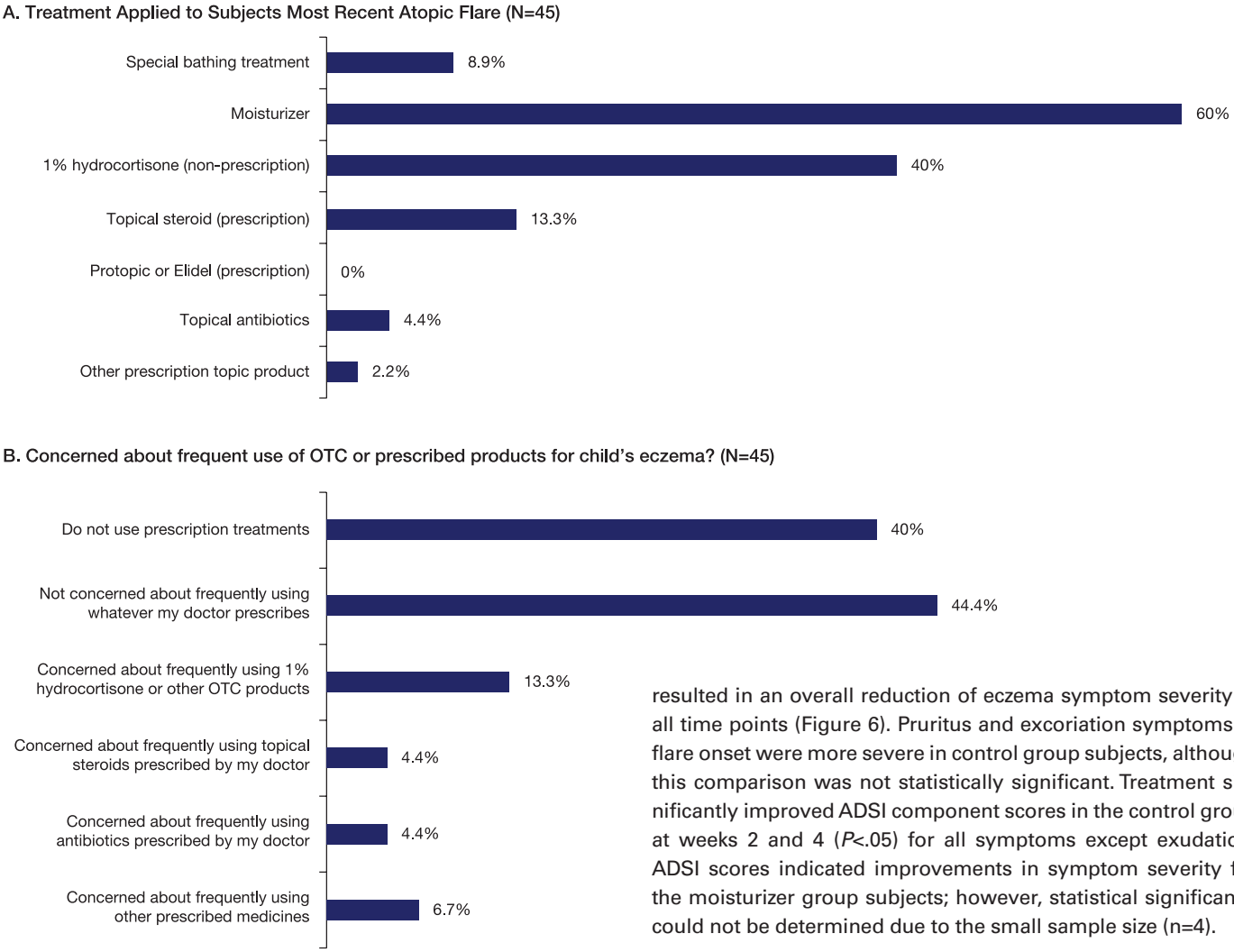
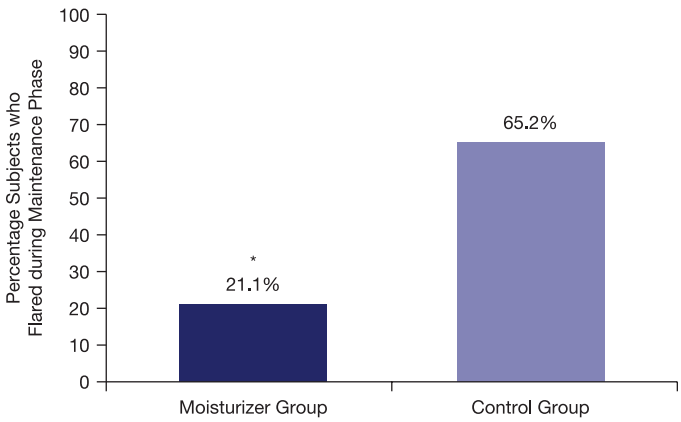


FIGURE 4. Proportion of subjects who flared during the maintenance phase. *P=.006.



resulted in an overall reduction of eczema symptom severity at all time points (Figure 6). Pruritus and excoriation symptoms at flare onset were more severe in control group subjects, although this comparison was not statistically significant. Treatment significantly improved ADSI component scores in the control group at weeks 2 and 4 (P<.05) for all symptoms except exudation. ADSI scores indicated improvements in symptom severity for the moisturizer group subjects; however, statistical significance could not be determined due to the small sample size (n=4).

Flare Treatment improved overall ADSI scores in the moisturizer group by 49.9% at week 2 and 84.2% at week 4 compared with baseline; however, significance could not be determined due to the small sample size. For the control group, ADSI scores improved after week 2 by 49.7% (P<.05) and by 66.7% after week 4 (P<.05) compared with baseline (Figure 7). There was no significant difference between groups for treatment effect on overall ADSI scores.

According to investigator assessment of flare improvement in the intent-to-treat population, 73.7% of flares showed moderate or marked improvement or had completely cleared at week 2, while 78.9% had improved or cleared at week 4.

Tolerability

Subject tolerability was assessed as either good or excellent for all tested formulations. One subject in the control group expe-

TABLE 2.

Summary Statistics of Time to Flare Between the Moisturizer and Control Groups

	All Subjects (n = 42[a])		Subjects With Flare (n = 19)	
	Moisturizer	Control	Moisturizer	Control
Median time to flare, days	>180	28	40.5	20
Mean time to flare, days	—	—	55	27.8
Minimum, maximum time to flare, days	28, >180	1, >180	28, 111	1, 98

[a]Excludes 3 subjects who flared during the washout phase.

FIGURE 5. Survival plot for flare-free subjects. Kaplan-Meier plot shows the percentage of subjects who remained flare-free over 6 months. At 6 months, the moisturizer group had a 44.1% reduction in risk of flare. Hazard ratio was 4.74 (95% CI, 1.57-14.38).

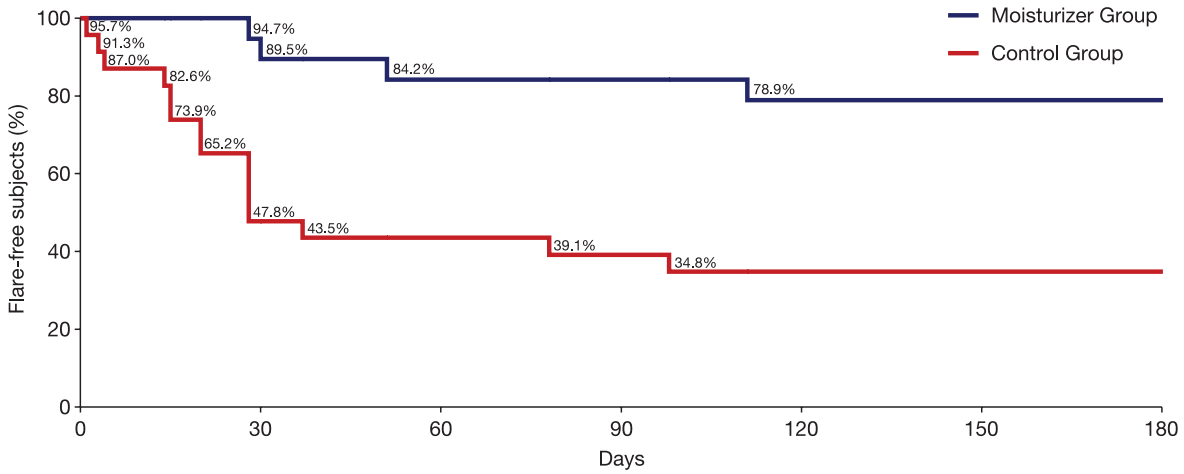
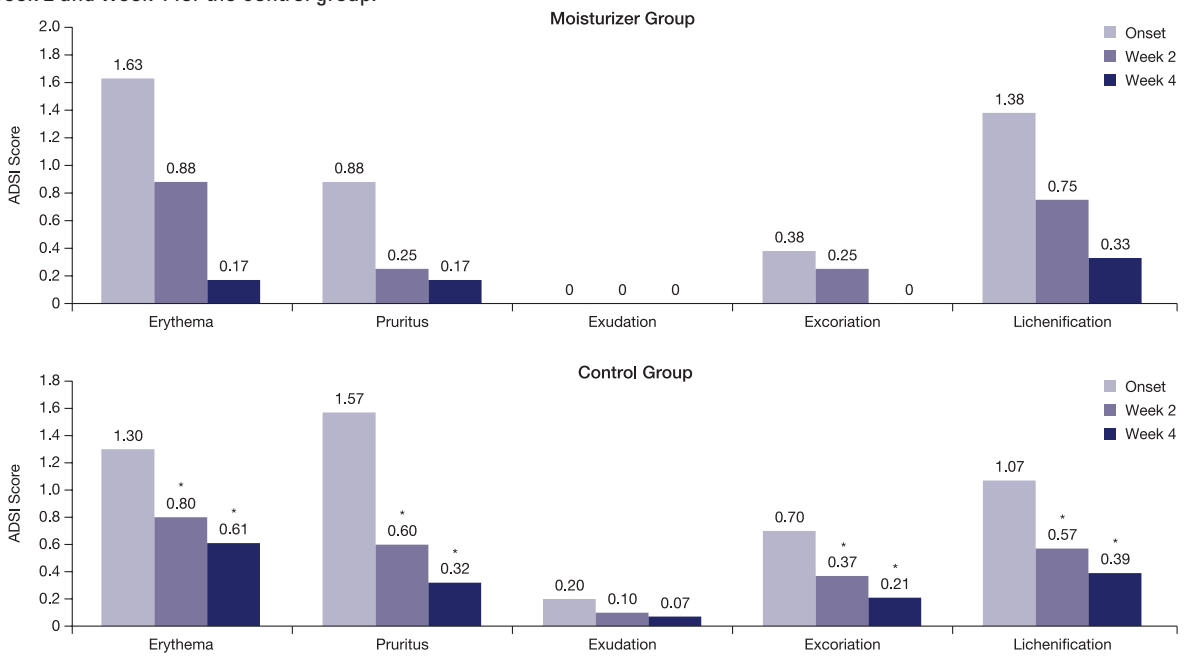
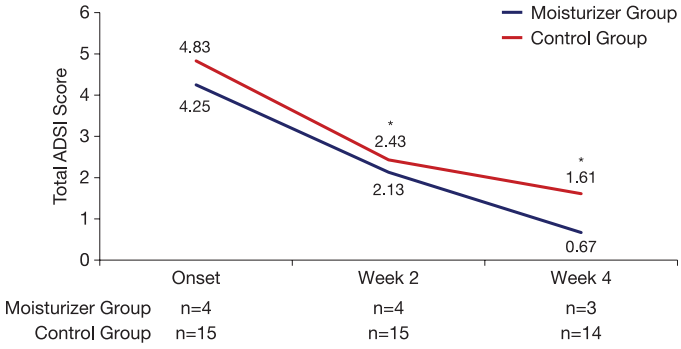


FIGURE 6. Atopic dermatitis symptom scores of flares during treatment phase. Mean ADSI symptom scores for the moisturizer group (n=4) and the control group (n=15) are shown. Statistically significant change from baseline was observed for erythema, pruritus, excoriation, and lichenification at week 2 and week 4 for the control group.



*P<.05. ADSI, Atopic Dermatitis Severity Index.

FIGURE 7. Total ADSI scores with flare treatment use. Mean total ADSI scores (0-15 scale) are shown. Statistical change from baseline was observed for the control group at week 2 and week 4.



*P<.05. ADSI, Atopic Dermatitis Severity Index.

rienced an adverse event (AE) during the treatment phase. The subject presented at the 2-week visit with worsening eczema on the back, chest, and stomach, whereby the subject was withdrawn from the study and treated with 1% hydrocortisone, and the eczema subsequently resolved.

DISCUSSION

A functioning skin barrier protects the body from infection, irritation, and TEWL. Characteristics of a healthy skin barrier include adequate hydration; natural moisturizing factor, lipid, and ceramide content; and an acidic pH. Barrier defects play a central role in the pathogenesis of AD. Consequently, daily moisturizing practices are important to support proper barrier function that can protect the skin from excessive bacterial colonization (especially by *Staphylococcus aureus*) and external irritants that provoke and exacerbate flares.[18] Daily moisturizing improves skin hydration, limits TEWL,[1] and can relieve pruritus,[19] helping to keep AD symptoms under control.

Reported rates of AD are high in children, and although approximately 70% of affected children outgrow their AD, their skin will remain susceptible to irritation throughout their lives.[1,2,10] The baseline questionnaire revealed that 82.1% of subjects had 3 or more flares in the year prior to the study. For treatment of their child's most recent flare, 26.7% of parents relied on advice from their pediatrician and 2.2% from their dermatologists; however, 68.9% of respondents (n=45) reported that they did not seek medical advice. This is not surprising, as it is unlikely that parents would take their child to a physician for every flare. In addition, 60% of parents used a moisturizer to treat their child's last flare. These results reinforce the need for education on the use of emollient moisturizers with proven efficacy to manage AD.

Due to the chronic, relapsing nature of AD, it is important to adopt skin care practices that can help minimize flare incidence and severity, including bathing with gentle cleansers and daily moisturizing with product formulations that are optimized to address the specific needs of atopic skin. Previous studies have examined the efficacy and tolerability of the Body Cream and Flare Treatment individually on adult and infant/child cohorts, but not as a skin care regimen for the management of AD.[16,17] In these earlier studies, Body Cream and Flare Treatment were found to significantly improve skin hydration and ameliorate AD symptom severity. Both products were safe and well tolerated in all subjects.

This clinical study tested the efficacy and tolerability of Body Cream and Flare Treatment when used in conjunction with a mild cleansing body wash formulation. Use of Body Cream and cleanser significantly reduced the incidence of flare compared with use of cleanser only (21% vs 65%, P=.006). In addition, treatment with Body Cream prolonged the flare-free interval for moisturizer group subjects, likely by helping improve and maintain barrier function,[16] validating Body Cream as a daily skin care product for the management of eczema. In subjects who experienced flare, baseline ADSI scores were notably higher for the control subjects than for the subjects receiving Body Cream, suggesting a further benefit of daily moisturizer use. Observed differences between groups in time to flare, the percentage of subjects experiencing flare, and the significant reduction in risk of flare reinforce the benefits of daily emollient therapy with moisturizers that have demonstrated clinical efficacy as a cornerstone in AD management.

Other studies of emollient treatment also support its use for the management and prevention of AD. In a study design similar to ours but conducted in adults, moisturizer (5% urea oil-in-water emulsion) was applied daily to a cleared flare for 6 months or left untreated.[20] The differences between moisturizer and control groups in the median time to flare (>180 days vs 30 days) and percentage of subjects experiencing flare (68% vs 32%) were similar to those in our study.[20] (It should be noted that 5% urea is not typically used for pediatric AD.) To further probe the relevance of daily moisturization in AD, two prevention studies were conducted in neonates with a family history of AD to determine whether early treatment with emollient therapy could reduce the risk of developing AD among high-risk neonates.[21,22] Newborns with either a parent or full sibling with AD were treated with daily emollient therapy within 1 to 3 weeks of birth for 6 months or were part of the control group that did not apply any topical products. In both studies, there was a statistically significant reduction in the relative risk of developing eczema of 32% to 50%.[21,22]

The study results also confirmed the efficacy of Flare Treatment in reducing active eczema symptom severity in infants and children. Flare Treatment was observed to be highly effective in reducing symptom severity, without concomitant medication, as demonstrated by significant decreases in ADSI scores from baseline after week 2 and week 4 in the control group, indicating the effectiveness of the acute therapy despite the lack of pre-flare skin care with moisturizer.

All products were well tolerated, both alone and in combination. Only one AE occurred during the study in a subject receiving cleanser along with Flare Treatment. No AEs occurred in subjects receiving cleanser and Body Cream.

These OTC formulations contain 1% colloidal oatmeal, licochalcone A, and ceramide 3, and were developed to help restore the acidic skin pH as well as to restore and maintain barrier function. An acidic pH is essential to healthy skin, inhibiting microbial growth and promoting the function of enzymes that regulate desquamation and barrier lipid maturation.[23,24] The skin pH of children with AD has been demonstrated to be higher relative to healthy counterparts,[25] and reestablishing an acidic skin environment is essential for repairing barrier function.

This study was the first randomized, controlled study testing the efficacy and compatibility of Body Cream and Flare Treatment—2 products designed and formulated to treat eczema. This study was limited by its small sample size, which may have influenced the statistical analysis of cohorts that contained only a few subjects.

CONCLUSIONS

Few OTC eczema formulations have been evaluated in infants and children as young as 3 months and demonstrated efficacy and tolerability. The Body Cream and Flare Treatment formulations offer parents/guardians and physicians efficacious nonsteroidal, OTC treatment options specifically developed for atopic skin. Results from this 3-phase study validate the use of these products as an effective, first-line treatment regimen for the management of AD, reducing the need for topical steroid intervention. Although beyond the scope of this study, it can be postulated that daily use of the Body Cream could reduce the number of flares a child experiences over a period of years, and could help reduce the need for, and cumulative exposure to, topical steroid treatments.

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DISCLOSURES

Teresa M. Weber PhD is an employee of Beiersdorf Inc, the manufacturer of Eucerin® Eczema Relief Body Crème and Eucerin® Eczema Relief Flare Treatment. Alexander Filbry PhD and Frank Rippke MD are employees of Beiersdorf AG. Frank Samarin MD and Michael J. Babcock MD have no conflicts of interest to declare.

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