

Nonsteroidal Treatment of Atopic Dermatitis in Pediatric Patients with a Ceramide-dominant Topical Emulsion Formulated with an Optimized Ratio of Physiological Lipids

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ABSTRACT

Atopic dermatitis is the most common chronic inflammatory skin condition seen in the pediatric population. In the United States, the prevalence rate of atopic dermatitis is 10 to 12 percent in children. A nonsteroidal, barrier repair product consisting of an optimal ratio of ceramides, cholesterol, and free-fatty acids has been demonstrated to be efficacious and safe in the treatment of atopic dermatitis in previous clinical trials. This report is a subgroup analysis of the efficacy and safety of this nonsteroidal, ceramide-dominant, physiological lipid-based topical emulsion used among 59 patients, three months to 16 years of age, with mild-to-moderate atopic dermatitis. Treatment success based on an Investigator Global Assessment rating of clear or almost clear was achieved by 58 percent of subjects after use of the ceramide-dominant, physiological lipid barrier repair emulsion for three weeks as monotherapy or in combination with another topical atopic dermatitis treatment. The severity of pruritus decreased markedly from Baseline to Week 3 overall regardless of disease severity at baseline. A large percentage of subjects (71%) reported satisfaction with clinical results. After three weeks of treatment, a significant number of subjects reported less worry about their atopic dermatitis compared to baseline. The results further support other publications that suggest a treatment approach that incorporates an optimized formulation of a skin barrier repair cream as an integral component of initial atopic dermatitis therapy, either as monotherapy or as part of combination topical therapy. (*J Clin Aesthet Dermatol.* 2011;4(12):25–31.)

Atopic dermatitis (AD) is a chronic-recurrent inflammatory dermatosis characterized by pruritus, eczematous lesions, xerosis, and lichenification. AD most often begins in infancy or early childhood, with approximately 90 percent of cases appearing in the first five years of life.¹ In the United States, the prevalence rate of AD is 10 to 12 percent in children, and AD is the most common chronic inflammatory skin condition seen in the pediatric population.^{2,3} It has been shown that the estimated number of pediatric visits for AD has been increasing annually in the United States.³

Childhood AD has a significant social and emotional

impact on the child and the family. Mothers of young children with AD have reported poor social support, stress related to parenting, and difficulty with discipline.⁴ It has also been shown that there is a positive correlation between the severity of AD and its impact on the quality of life of pediatric patients and their families.⁵ Parents of children with AD are commonly plagued by several persistent “worries,” including concerns regarding what triggers disease flares in their child, the costs of care, proper use of medications, and their child’s health, well-being, and self-esteem in the long-term.¹ Parents also commonly worry about the use of topical corticosteroids and their side effects. In one questionnaire-based study, 73

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percent of participants worried about using topical corticosteroids on their own or their child's skin, leading to nonadherence in 24 percent of individuals.⁶

In one study assessing quality of life (QOL) of children with AD aged 5 to 10 years, QOL scores were directly correlated to AD severity as assessed by the investigator, and changes in the QOL scores were closely related to changes in AD severity scores.⁷ A study involving in-depth interviews with parents of young children with AD demonstrated that sleep disruption and pruritus/scratching are the most prevalent physical symptoms experienced by affected children, with more than half of the AD effects on children directly or indirectly related to pruritus.¹ Pruritus often leads to an "itch-scratch" cycle that can compromise the epidermal barrier, resulting in increased transepidermal water loss (TEWL), visible signs of xerosis, microbial colonization, especially with *Staphylococcus aureus*, and secondary infection.⁸ The physical changes in AD can affect pediatric patients in a variety of ways, including lack of sleep, an inability to focus in school, behavioral problems, low self-esteem, stress, and anxiety. It has been reported that sleep disturbance (e.g., poor sleep, lack of sleep) occurs in 60 percent of patients as a result of frequent and often intractable pruritus that is such a consistent and predominant symptom of AD.⁹ In AD, documented sleep dysfunctions include delayed onset of sleep, multiple awakenings, and reduced sleep efficiency.⁴ As expected, the natural consequence of poor sleep is adverse impact on daytime behavior and productivity.

AD also has a significant financial impact on the family of an affected child. It has been estimated that the overall annual cost associated with a given child with severe AD is \$4,500.¹⁰ Treatment strategies targeted toward management of symptoms, improvement of epidermal barrier function, and prolongation of the time between flares of AD help to decrease the cost of treatment.¹⁰

The pathophysiology of AD is not fully understood, though it is characterized by a complex interaction of genetics, aberrations in immune response, and impairment of stratum corneum (SC) barrier functions, including the permeability barrier and the antimicrobial barrier.¹¹ Early treatment approaches, based primarily on the hypothesis that AD is primarily immunologically driven, emphasized the suppression of Th2-mediated inflammation and pruritus. As a result, discussions regarding treatment heavily emphasized the use of topical glucocorticoids (GC) and/or topical calcineurin inhibitors (TCI), with little mention of addressing SC abnormalities as a primary goal other than the suggestion to use gentle skin care adjunctively. It is well accepted in dermatology that greater vigilance regarding potential adverse reactions is warranted in the pediatric patient subset. TCIs are not indicated based on United States Food and Drug Administration (FDA) approval for patients less than two years of age, and many topical GCs have suggested age restrictions in their approved package inserts. Also, due to body surface ratio considerations in infants and small children, the risk of hypothalamus-pituitary-adrenal (HPA) axis suppression is of greater concern, especially with diffuse

application and/or prolonged duration of use.¹²

A hypothesis that suggests that impairment of the epidermal permeability barrier participates significantly in the pathogenesis of AD is supported by confirmation of several abnormalities of the SC that are innate to AD and are present in actively eczematous, xerotic-appearing, and normal-appearing skin of AD patients. A major component of SC barrier dysfunction in AD that is well documented is a decrease in major SC lipids that comprise the intercellular lipid membrane (bilayer), especially certain ceramide subfractions.¹³ When increased TEWL reaches a critical threshold, a cytokine cascade is initiated, which leads to cutaneous inflammation as a means to counter increased epidermal permeability, which more easily allows for the transcutaneous passage of microbial organisms, haptens, allergens, and irritants ("outside-in theory"). If one accepts that individuals with AD are inherently burdened with abnormal epidermal barrier function, a concept that is well substantiated scientifically, then addressing this component AD becomes an integral part of the therapeutic management of AD. In other words, comprehensive management of the patient with AD would need to include consistent use of a well-formulated barrier repair therapy during periods of both eczema exacerbation and quiescence, along with other therapies that are needed to manage eczema flares depending on the severity of a given episode.

A specific ceramide-dominant, physiological lipid-based barrier repair topical emulsion (EpiCeram® Skin Barrier Emulsion), referred to hereafter as CDPL barrier repair emulsion, is available as an FDA-cleared prescription product that is nonsteroidal and not restricted in its use by age or cutaneous location. The CDPL barrier repair emulsion incorporates a physiological 3:1:1 molar ratio of ceramides, cholesterol, and free fatty acids, which is believed to be optimal, as this ratio mirrors the endogenous intercellular lipid membrane of the SC and has been shown to repair SC integrity and function.¹⁴ In addition to assisting in the restoration of the relative amounts of the three major SC lipid components in the endogenous intercellular lipid membrane of the stratum corneum, this product also helps to normalize the pH of the skin. The CDPL barrier repair emulsion has demonstrated an excellent safety profile with no known significant risks outside of occasional transient tingling upon application. As stated earlier, the CDPL barrier repair emulsion can be used by all age groups and on any cutaneous anatomic locations, including the face and intertriginous areas, with no limitation on the duration of treatment.

The efficacy of the CDPL barrier repair emulsion for the treatment of AD has been previously demonstrated in a prospective, randomized, controlled, investigator-blind clinical trial compared to fluticasone propionate cream 0.05% in pediatric patients with moderate-to-severe AD.¹² The current study is a subgroup analysis of a large, community-based, open-label, interventional study performed with the goal of expanding upon the results reported earlier by evaluating the efficacy of the CDPL barrier repair emulsion in "real world" outpatient dermatology practice settings in patients with mild-to-moderate AD and with a wide range of

demographic characteristics.¹⁵ This report focuses on results for pediatric subjects 3 months to 16 years of age. The original study included 207 subjects, most of whom were adults (71.5%).

MATERIALS AND METHODS

Study design and procedures. This study was an open-label, community-based trial conducted at 50 sites in the United States. Investigators for the study were required to be dermatologists currently licensed to practice in the state where the study was being conducted and to have a community-based medical practice in which they saw a large number of patients with mild-to-moderate AD. The study protocol and informed consent form were approved by an Institutional Review Board operating in compliance with federal regulations. Subjects of all ages and races with mild-to-moderate AD were eligible for enrollment. Data from subjects between the ages of 3 months to 16 years are presented here. Upon study enrollment, any current medication for AD was discontinued. Subjects were not allowed to have had any prior treatment with the CDPL barrier repair emulsion. Demographic data was collected including age, race, sex, location of AD, flare frequency, year of AD diagnosis, medical conditions associated with atopy (seasonal rhinitis, asthma, and/or food allergies), and family history of AD.

Subjects were instructed to apply the CDPL barrier repair emulsion to affected areas and commonly involved sites of AD (e.g., antecubital region, popliteal region) twice daily, approximately every 12 hours, for a duration of three weeks. Subjects were also given a prescription for another AD medication, chosen by the investigator, and instructed to use this medication along with the CDPL barrier repair emulsion as combination therapy, only if their condition worsened significantly and was not adequately controlled by the barrier repair study product alone. The majority of subjects (66%) completed the entire three weeks of the study using only the CDPL barrier repair emulsion as monotherapy, without ever using the prescribed additional medication, while 34 percent of subjects used combination topical therapy (CDPL barrier repair emulsion plus the prescribed medication). For those subjects who used the additional prescribed medication, there was an average use of seven days during the study. The other prescribed topical treatments used consisted predominantly of topical corticosteroids of low potency (7% of total N), mid-potency (22% of total N), or high potency (3% of total N), with one subject using an unknown prescribed medication.

At Baseline and at the Week 3 visit, each investigator assessed the severity of AD using the Investigator Global Assessment (IGA) scale (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe), and each subject (or parent) rated the severity of pruritus on a scale of 0 to 4 (0=absent [no itching], 1=minimal [rarely aware of pruritus, only present when relaxing and lasts for a very short time], 2=mild [occasionally aware of pruritus, not annoying], 3=moderate [often aware of pruritus, sometimes disturbs sleep and daytime activities], and 4=severe [constant pruritus,

TABLE 1. Subject demographics

	MEAN	RANGE
Age (years)		
	7.4	3 months to 16 years
	NUMBER OF SUBJECTS	%
Gender		
Male	27	41.5
Female	38	58.5
Race		
Caucasian/Latino white	42	64.6
Asian	5	7.7
African American/Latino Black	11	16.9
Other	7	10.8

distressing, frequent sleep disturbance, interferes with activities]). Parameters related to QOL were also assessed at both visits by the use of questions regarding general worry and negative impact on daily activities. At the Week 3 visit, subjects (or parents) reported their perceived improvement in AD, satisfaction with the clinical results, need for the prescribed additional medication, and adverse events. Investigators also reported their satisfaction with the clinical results at Week 3.

Statistical methods. All statistical analyses were performed on the intent-to-treat (ITT) data set at the 0.05 alpha level, two-tailed. The primary efficacy variable was the change from baseline in IGA at Week 3, which was analyzed using a paired *t*-test comparing IGA scores at Baseline and Week 3. IGA was also dichotomized as success (clear or almost clear) or failure and the proportion of subjects with IGA success was summarized and analyzed using chi square. Other variables were dichotomized as described below. For categorical variables, chi-square test or the McNemar test was used as appropriate.

RESULTS

Subject characteristics. Informed consent was obtained for 65 subjects enrolled, with 59 pediatric subjects completing the study and six subjects lost to follow up. The demographic characteristics of subjects are shown in Table 1. There were slightly more female subjects (58%) and the majority of the subjects were Caucasian (65%), with a mean age of 7.4 years (range, 3 months–16 years).

Disease characteristics for the pediatric subjects are summarized in Table 2. Subjects had either mild (49%) or moderate (51%) severity of AD at baseline. For 31 percent of

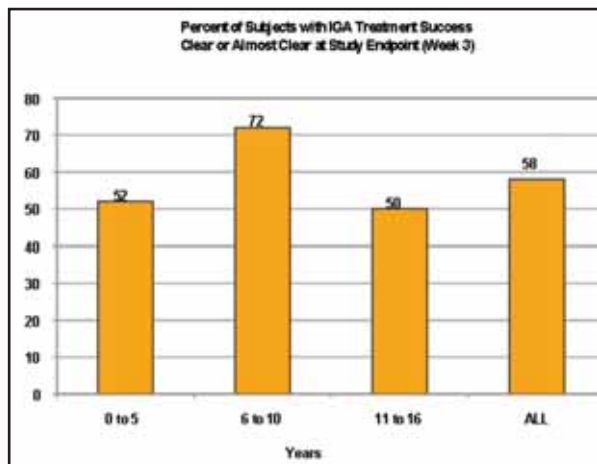


Figure 1. Percent of pediatric subjects by age group with IGA-based treatment success (clear or almost clear) at study endpoint (Week 3)

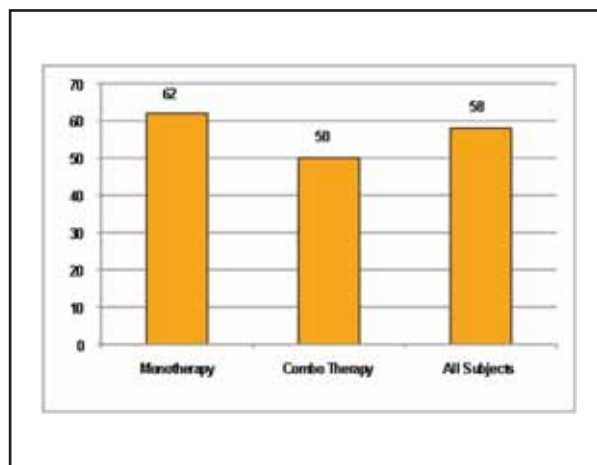


Figure 2. Percent of subjects with IGA-based treatment success (clear or almost clear) at study endpoint (Week 3)



Figure 3. Mean pruritus score at Baseline and study endpoint (Week 3). Comparisons made to pruritus severity rated at Baseline as mild, moderate, or severe; $*p < 0.05$ (at study endpoint as compared to baseline)

TABLE 2. Disease characteristics

CHARACTERISTIC	NUMBER OF SUBJECTS (N=65)	%
Mild disease	32	49.2
Moderate disease	33	50.8
with family history of AD	20	30.8
No other associated conditions	38	58.4
with seasonal rhinitis (hay fever)	9	13.8
with asthma	11	16.9
with food allergy	14	21.5
AD flare		
• one or more/month	56	86.2
• less than one /month	9	13.8
AD location		
• leg	51	78.5
• arm	48	73.8
• trunk	37	56.9
• head/neck	31	47.7
• hand	13	20.0
• foot	10	15.4

the subjects, there was an immediate family member, most often the mother or father, with a history of AD. No atopy-associated disorders were reported for 58 percent of subjects, while 14 percent of subjects also had seasonal rhinitis (“hay fever”), 17 percent had asthma, and 22 percent reported having food allergy. Eighty-six percent of subjects reported that their AD flared one or more times a month while 14 percent of subjects reported flaring less than one time per month. The most common locations of disease were on the legs (78% of subjects) and arms (74% of subjects), with the active lesions of eczema commonly noted on the trunk (57% of subjects) and the head/neck (48%). At Baseline, 64 percent of subjects suffered from moderate or severe pruritus.

Efficacy results. Figure 1 shows success with IGA across age groups within the pediatric subgroup. Fifty-eight percent of all pediatric subjects were clear or almost clear at Week 3 and thus were rated as having achieved “treatment success” based on IGA according to the study protocol. Sixty-two percent of subjects who used monotherapy achieved success with IGA at Week 3, while 50 percent of subjects who used topical combination therapy achieved success with IGA at

Week 3 (Figure 2). There was no statistical difference in success rate between the combination therapy and monotherapy groups. Within the subgroup of subjects that achieved success with IGA, 71 percent used monotherapy and the group had a mean baseline IGA of 2.5. Subjects with success using combination therapy had a similar mean baseline IGA of 2.4. The overall mean IGA at baseline for the pediatric subgroup was 2.49, which was statistically significantly reduced to a mean of 1.37 at Week 3 ($p<0.001$).

Figure 3 displays the change in mean pruritus score, as reported by study subjects during the previous 24-hour period, from baseline to Week 3, and classified based on initial severity of pruritus at Baseline. The severity of pruritus decreased significantly ($p<0.05$) from Baseline to Week 3 for all Baseline severities.

Satisfaction with clinical results. The investigators were satisfied with the clinical results observed at Week 3 for 73 percent of the subjects (very satisfied for 41% of subjects, satisfied for 17% of subjects, and somewhat satisfied for 15%) (Figure 4). Seventy-one percent of subjects were satisfied (42% were very satisfied, 12% were satisfied, and 17% were somewhat satisfied) with their clinical results as compared to Baseline (Figure 5). Eighty-one percent of subjects believed that their AD had improved as compared to Baseline (Figure 6).

Quality-of-life assessments. At Baseline and Week 3, subjects were asked to rate their amount of worry about their AD and also how much negative impact their AD created on daily activity. Significantly more subjects (80%) reported no worry or a little worry about their AD at Week 3 compared to 53 percent at Baseline ($p=0.0006$) (Table 3). There was no significant difference ($p=0.0522$) in the percentage of subjects reporting no or minimal negative impact on daily activities after three weeks of using CDPL barrier repair emulsion treatment compared to Baseline (73% vs. 84%) (Table 5).

Adverse events. Three subjects reported four adverse events that were related to treatment (mild pain, application site irritation and pruritus, moderate skin irritation). One other subject reported worsening of AD during treatment. There were no serious AEs.

DISCUSSION

Since most cases of AD begin in infancy or early childhood, it is important to determine a course of treatment in this population that is efficacious, easy to use, and with minimal potential for side effects. With the heavy social, emotional, and financial impact of childhood AD on patients, parents, and other family members, it is believed that reversal of epidermal barrier impairment and restoration of SC function from the outset of treatment of a flare is important to integrate into management of all patients with AD. The

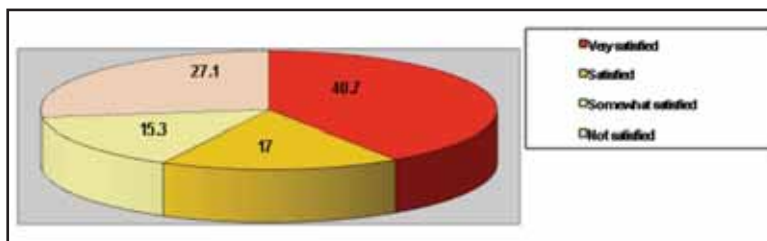


Figure 4. Investigator satisfaction with clinical results at study endpoint (Week 3). Percentage of subjects reaching a designated satisfaction rating based on investigator assessment

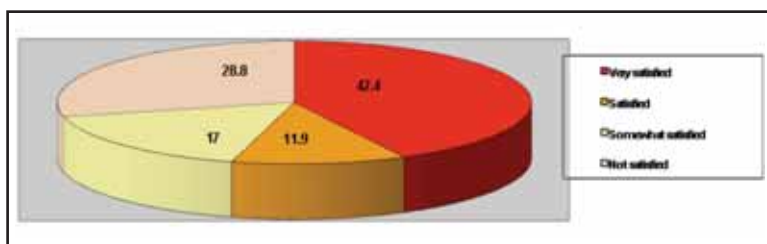


Figure 5. Subject satisfaction with clinical results at study endpoints (Week 3). Percentage of subjects reporting that they reached a designated satisfaction rating

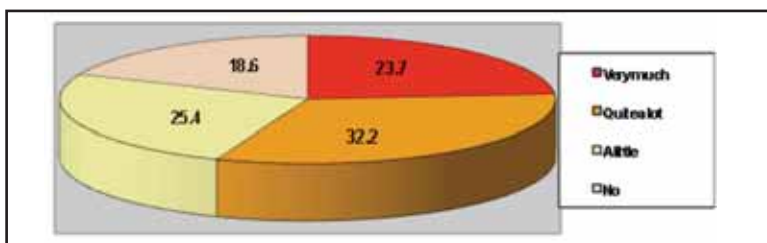


Figure 6. Percentage of subjects with improvement in atopic dermatitis at study endpoint (Week 3) [AUTHOR: Please check the color key for Figs 4-6. In Fig 6, the words seem to run together. Do you want to send a new Fig or have me fix?]

results of this subset analysis and other studies support the use of the CDPL barrier repair emulsion for this purpose.^{12,15}

In this study, the efficacy, tolerability, and level of satisfaction associated with use of a CDPL barrier repair emulsion in the setting of ambulatory dermatology practice was evaluated in pediatric patients with mild-to-moderate AD. To achieve this objective, data from a subgroup of 65 pediatric subjects from a previous study were analyzed.¹⁵ Data were gathered from the perspective of the practicing clinical dermatologist, with 50 dermatologists from community-based medical practices enrolling subjects and evaluating response.

A topical treatment approach with first-line use of CDPL-based topical emulsion as an epidermal barrier repair product was used in this study. This treatment approach is based on the permeability barrier hypothesis of AD pathogenesis, which suggests that the AD of patients with mild disease may usually be controlled with the use of an epidermal barrier repair product as monotherapy, while patients with moderate or severe disease may require an additional medication, such as a topical corticosteroid, as combination therapy. To simulate the treatment approach based on the permeability

TABLE 3. Percent of subjects reporting amount of worry and impact on daily activities at Baseline and Week 3

	BASELINE	WEEK 3	p VALUE
No worry or a little worry	53	80	0.0006
No negative impact or a little negative impact on daily activities	72	84	0.0522

barrier hypothesis, subjects were supplied with a tube of the CDPL barrier repair emulsion at the Baseline visit and were also given a prescription for an additional AD treatment, chosen by the investigator, to be used at the discretion of the subjects (or their parents). The subjects (or parents) could decide whether to supplement the use of the CDPL barrier repair emulsion with the additional prescribed treatment (combination therapy) based on whether or not they found the CDPL barrier repair emulsion to be effective alone in treating their AD. It is believed that if the severity of AD was not adequately controlled by the CDPL barrier repair emulsion alone within a reasonable time period, especially with pruritus, that most individuals (especially parents) would procure the additional treatment in order to expedite response to treatment. The majority of subjects or their parents (66%) chose not to use the prescribed additional medication and used only the CDPL barrier repair emulsion during the three-week study period.

More than half of the pediatric subjects (58%) achieved “treatment success” based on IGA (clear or almost clear scores) after three weeks of treatment with the CDPL barrier repair emulsion either as monotherapy or in combination with another treatment. There was no significant difference in success rate between the monotherapy and topical combination therapy study groups, and most subjects (71%) with success were on monotherapy and had the same severity of disease as the subjects who used combination therapy.

Rates of overall satisfaction (approximately 70%) were higher than the rate for clinical success, implying that clinical efficacy was not the sole contributing factor to satisfaction with treatment in this study. After three weeks of medication use, subjects had significantly less worry about their AD than they did at Baseline. Perhaps the high rate of subject satisfaction could partially be a result of less worry about AD.

There was a significant reduction in mean severity of pruritus from Baseline to Week 3 for all categories of Baseline pruritus severity, and there were markedly fewer subjects with moderate or severe pruritus at Week 3 than at Baseline. The reduction in pruritus after just three weeks is important, as this reduction could lead to positive changes in sleep behavior for the child as well as the parents. Positive change

in sleep pattern could result in improved daytime behavior and mood.

The excellent safety profile of this CDPL barrier repair emulsion has been noted in other studies and was again demonstrated in this study, an important factor for use in the pediatric population among clinicians and parents or guardians.^{12,15}

Potential limitations of this study are recognized by the authors. These include only a single follow-up visit after the Baseline visit, which served as the study endpoint, the relatively short study duration (3 weeks), and the relatively small number of pediatric patients in the subgroup analysis. Success rates may have been influenced to some degree because the study was open label

and not vehicle controlled. In addition, satisfaction was not specifically defined in the protocol and analysis of factors that correlate with satisfaction could identify important considerations that drive whether or not patients are pleased with their therapy.

In conclusion, this study illustrates that this CDPL barrier repair emulsion is efficacious, either with or without additional topical AD therapy, in the treatment of mild-to-moderate AD in pediatric patients. In addition, treatment with this product resulted in high levels of investigator and patient satisfaction. The results from this subgroup of pediatric patients are similar to those seen in earlier studies looking at treatment with this CDPL barrier repair emulsion in AD subjects of all ages. Additionally, the results gleaned from this subgroup analysis also support the treatment approach of universally incorporating a targeted epidermal barrier repair product to alleviate the permeability abnormalities of the SC that are innate to all patients with AD. Other additional prescription medications, such as topical GCs, may be used at the discretion of the clinician for AD patients presenting with a flare that is severe enough to necessitate combination therapy in order to achieve a prompt and adequate response, such as patients with moderate-to-severe AD.

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