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Efficacy of Topical Botanical Treatment of Children With Mild to Moderate Atopic Dermatitis

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ABSTRACT

Objective: The study was conducted to determine the efficacy of the botanical combination incorporated in Kamedis Eczema Therapy Cream (the test product) for children with mild to moderate atopic dermatitis.

Design: The study was designed as an interventional, multi-center, double-blind, randomized, controlled study.

Setting: Children subjects were a sub-population of the 108 combined population of adults and children evenly randomly divided into three treatment groups: test product, vehicle and comparator. The vehicle used was the identical test product without the botanical combination while the comparator was a leading OTC brand in the US market. All three groups used the same Kamedis body wash followed by one of the three randomized treatment creams for the affected areas.

Participants: Thirty-nine (39) children subjects with uncomplicated, stable, mild to moderate atopic dermatitis recruited and qualified for the study, 24 female and 15 male, ages varying between 3 to 18.

Measurements: Investigators assessed the severity of each subject using the Investigator Global Assessment (IGA), affected Body Surface Area (BSA) extent evaluated parameters at each of the visit days 0, 7, 14, and 28. Subjective symptoms of pruritus and insomnia were evaluated by the patient or their legal guardian. The SCORAD and EASI indexes were calculated based on the collected parameters.

Results: The test product demonstrated an improvement in all evaluated and calculated clinical parameters over the vehicle at the end of the treatment duration, proving the validation that the test product is much more effective and beneficial than the vehicle. The test product reached 40% of 'clear' IGA subjects out of the enrolled subjects and 60% out of the 'clear' and 'almost clear' IGA subjects comparing to 8% and 38%, respectively, with the vehicle, presenting a clear advantage over the vehicle. The BSA improvement comparison analysis of the test product over the vehicle yielded *P* value of less than 0.05, which is statistically significant. The SCORAD and EASI indexes also showed an advantage of the test product versus the vehicle at week 4.

Conclusion: The study results validate that the botanical combination is the key factor for the efficacy and improvement of the AD symptoms within this population of children.

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INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease and the most common chronic skin disease in children, with a lifetime prevalence of 10-20%.[1] AD usually appears in early infancy and is characterized by pruritus and erythematous papules.[2] In severe cases, intense pruritus and scratching may lead to secondary infection.[1] AD is usually associated with other atopic diseases (asthma, allergic rhinitis). The clinical pattern of AD varies with age. The childhood phase typically occurs from 2 years of age to puberty. Although AD is a chronic disease, it resolves in about 60% of patients before adulthood.[3] In 45% of children, the onset of AD occurs during the first 6 months of life, during the first year of life in 60% and before the age of 5 years in at least 85% of affected children. In those children with onset before the age of 2 years, 20% of the population will have persisting manifestations of AD, and 17% of them on the other hand will experience intermittent symptoms by the age of 7 years. Older children are less likely to have the exudative lesions commonly seen in infancy and instead exhibit more lichenified papules and plaques representing the severity of the chronic disease and involving the hands, feet, wrists, ankles, antecubital and popliteal regions.[4]

Without an understanding of the complex and multifactorial pathogenesis of AD, treatment can be difficult and often unsatisfactory. When the structural integrity of the epidermal barrier is compromised by injuring the aggregation of keratin filaments supporting the skin barrier, as in a mutation, pathogens or allergens, toxins are able to pass through the hyperpermeable barrier.[5-7]

Currently, there is no cure for the disease. Management of AD focuses on controlling the severity and duration of AD symptoms. In mild to moderate cases, treatment includes reduction of exposure to triggering factors and topical application of emollients and steroid-free barrier creams as well as topical corticosteroids. In more severe cases, the condition is often treated with systemic corticosteroids and immunosuppressive agents such as methotrexate, cyclosporin, and azathioprine. Due to their potential side effects, these treatments are avoided for long-term use, especially in young children.[8-13]

Kamedis Eczema Therapy Cream (the test product) is a non-steroidal homeopathic emulsion based on botanicals, which is especially formulated to manage the symptoms of various dermatoses such as atopic dermatitis, contact dermatitis, nummular dermatitis, hand dermatitis, radiation dermatitis, and burns. This emulsion protects the skin from further irritation and maintains a moist environment.

The test product was developed to include a combination of six botanicals: *Rheum palmatum, Sanguisobra officinalis, Ailanthus altissima, Scutellaria baicalensis, Cnidium monnieri, Glycyrrhiza glabra.* These botanicals are known to have significant anti-inflammatory and anti-allergic activities that assist in the relief of AD symptoms.[14-15] The purpose of this research was to validate the effectiveness of the botanicals for the treatment of AD. This paper is focused on examining the efficacy of pediatric population only. In order to meet this goal, a vehicle product formula was developed to be tested in comparison with the botanical test product. The vehicle product was designed to include all ingredients in the same relevant percentages as in the test product, including homeopathic Sulphur 12x, without the combination of the six mentioned botanicals.

The analytical evaluation in this research was performed by using Investigator Global Assessment (IGA), Body Surface Area (BSA), Scoring Atopic Dermatitis (SCORAD) calculated index, and Eczema Area and Severity Index (EASI) index. The IGA score is based on the severity of erythema, infiltration, population, number of lesions, and oozing and is selected by an overall appearance of the lesions at a given time point. The involved surface area that composed the total BSA in AD is a crucial factor in grading the degree of severity. The BSA is presented as a percentage index for the involved lesional features and locations.[16] The SCORAD index was evaluated by taking into consideration the subject evaluation of insomnia and pruritus.[17] EASI index was calculated using the intensity and extent symptoms.

METHODS

Thirty-nine (39) children with uncomplicated, stable, mild to moderate atopic dermatitis were recruited and qualified for the study, 24 female and 15 male, ages 3 to 18. The enrolled children population composed 39.4% of a wider atopic dermatitis study population including 99 subjects who completed the trial.
The trial was designed as an interventional, multi-center, double-blind, randomized, controlled study, conducted under an Institutional Review Board (Integreview IRB, Austin, TX, USA). A signed informed consent form and a photographic release form were obtained from the subject's parent/s prior to performing any study procedure.

Subjects enrolled according to the inclusion criteria of 2 years of age and older, mild to moderate atopic dermatitis that met the Hanifin and Rajka criteria, and stable for 7 days. Pregnant females were not included in the study and a negative urine pregnancy test result was required for each of the visits of every female subject with childbearing potential. The exclusion criteria list included another dermatological disease that could interfere with clinical evaluation, previous history of allergy to cosmetic products or specific relevant ingredients, treatment by topical or systemic immunomodulators for atopic dermatitis or steroids 14 days prior to the beginning of the study, treatment by phototherapy 28 days prior to the beginning of the study, any experimental treatment within 14 days prior to the beginning of the study and expected extensive sun exposure during the study period.

All subjects were randomly divided into three treatment groups, 10 subjects for the tested product, 13 subjects for vehicle and 16 for the comparator group. The vehicle was the test product without the botanical combination and the comparator was a leading OTC brand in the US market. All three groups used Kamedis body wash and one of the three treatment creams for their affected areas.

Subjects were requested to apply the treatment product twice daily following Kamedis wash, as per instructions, morning and evening.

The study duration was 28 days with visits occurring at baseline (day 0), day 7, day 14, and day 28. Subjects underwent AD lesion assessment evaluated by the investigator at each of the visits. Digital photos were taken of the affected lesions at each visit in one of the study sites (17 subjects) with a Nikon D-90 camera in a Canfield 3-point head mount with an IntelliFlash system and a consistent f-stop for reproducibility at all time points.

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The investigators assessed the severity of each subject using Investigator Global Assessment (IGA) and additional severity score evaluation parameters at each visit. For the IGA parameter, the following grading scale was used: 0=Clear, 1=Almost Clear, 2=Mild, 3=Moderate, 4=Severe, and 5=Very Severe. The BSA was estimated by assessing the affected percentage of the following body areas: Head, trunk, upper limbs, and lower limbs. For mild to moderate AD the affected BSA is typically lower than 10%. The SCORAD Index is defined by the following formula A/5 + 7B/2 + C where A is the extent (0–100), B is the intensity (0–18) and C are the subjective symptoms (0–20). The maximal score of the SCORAD Index is the number 103 and reflects the most severe disease. The extent parameter (A) is comprised of the anterior/posterior drawing of the patient's lesions. The intensity part of the SCORAD index (B) consists of six items: erythema, oedema/population, excoriations, lichenification, oozing/crusts, and dryness. Each item can be graded on scale 0-3. The subjective item (C) include the summation of the subject's daily pruritus and sleeplessness. The maximum subjective score is 20. An EASI score is used to measure extent (area) and severity of AD. EASI score includes only inflamed areas and does not include dryness or scaling. There are four body regions for EASI Scoring in children. For head and neck, the face occupies 33%, the neck 33%, and the scalp 33%. For the trunk region, the anterior torso occupies 55% and the back 45%. For the upper limbs each arm occupies 50% of the upper region.[17]

The statistical analysis used a two-way analysis of variance (ANOVA) with visit and treatment/control as main factors and the interaction between them. A major interaction would mean that the difference between the chosen observed treatments is not similar across visits. Factors with *P*-values less than 0.05 are considered statistically significant. For each parameter, the original scores were transformed to percentage of improvement by calculating the percentage of increased score compared to the score measurement of each patient at baseline (day 0).

RESULTS

39 children with ages ranging from 3 to 18 were enrolled and completed the study. No adverse events occurred during the course of the trial.

Demographics of the subjects are presented in Table 1. No significant statistical difference was observed in IGA, severity score and body evaluated parameters as well as calculated indexes between each of the treatments groups in the baseline (BL) visit (day 0), however, a slight trend of more severe subjects was included in the tested product group compared to the other two groups (Figure 1, Figure 2, and Figure 3).

At each visit the investigator assessed the subject's IGA, BSA and extent and intensity of the evaluated parameters. The subject or the legal guardian rated the appropriate visual analogue scale (VAS) for pruritus or itch intensity as well as sleep disturbance. The IGA is presented in severity index score evaluation. The number of subjects reaching the 'clear' or '0' score evaluation was counted per each treatment and the percentage was

TABLE 1.

Subject Demographic Characteristics	
Characteristic	**Value**
Age range (years)	3-18 years old
Sex	F - 24 (62%)
	M - 15 (38%)
Race	African American - 26 (67%)
	Caucasian - 13 (33%)

FIGURE 1. BSA raw data collected per each visit in weeks duration.

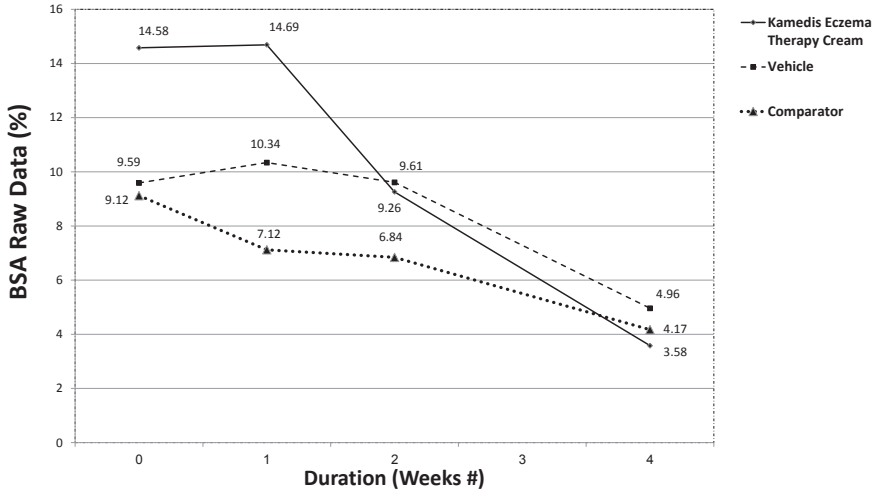


FIGURE 2. BSA improvement per each visit in weeks duration.

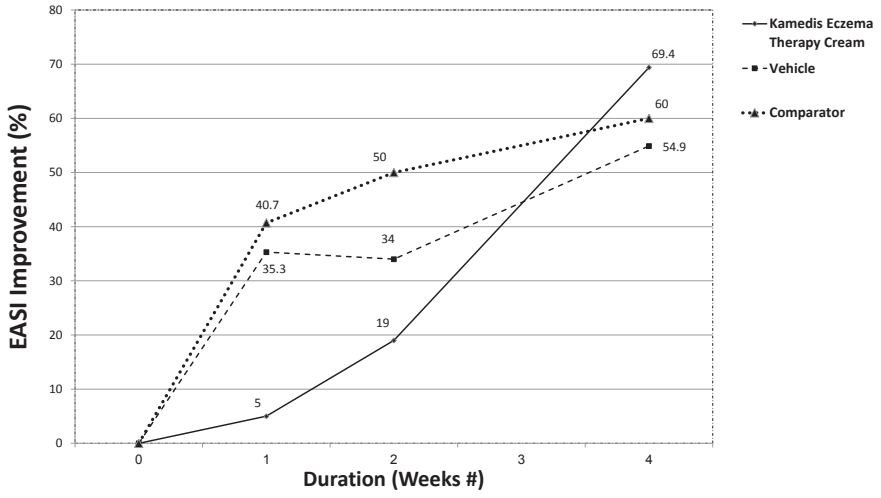


FIGURE 3. SCORAD raw data calculated per each visit in weeks duration.

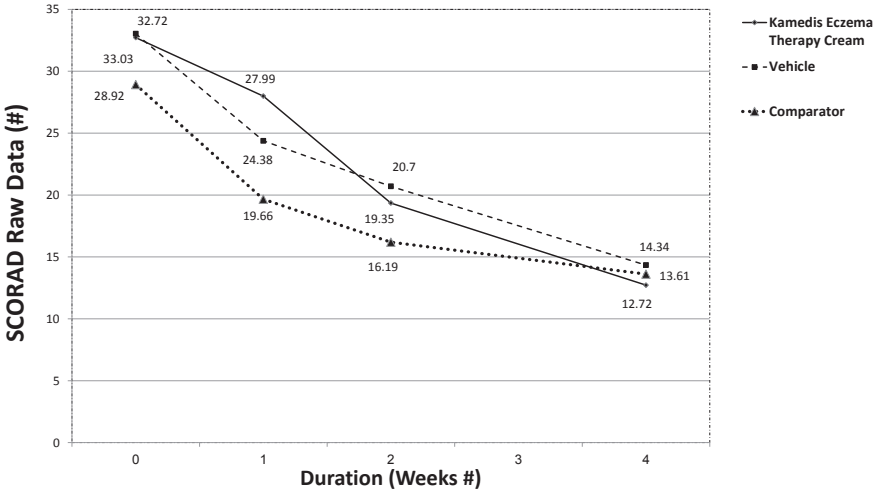


FIGURE 4. SCORAD improvement per each visit in weeks duration.

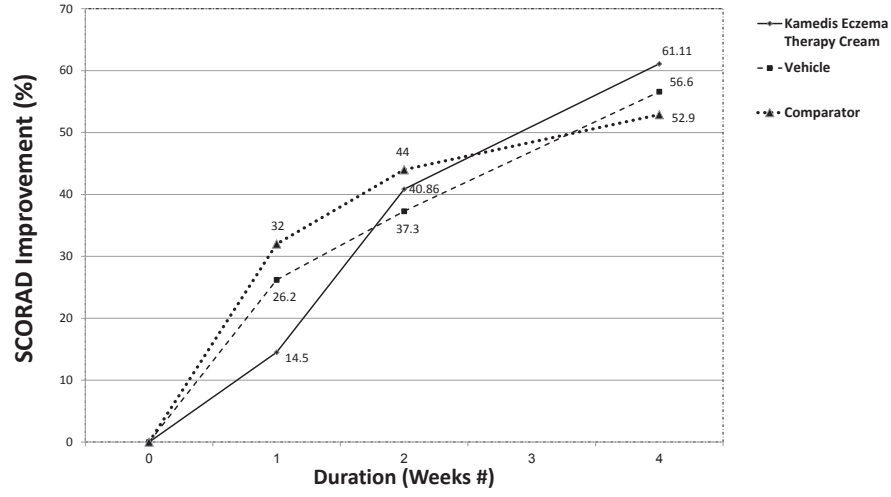


TABLE 2.

Clear Score IGA Percentage of Enrolled Subjects			
Product	**# of 'Clear' Subjects (IGA=0) following 4 weeks of treatment**	**Total # of Subjects who concluded the study**	**Percentage of 'Clear' out of 'Total' (%)**
Kamedis Eczema Therapy Cream	4	10	40
Vehicle	1	13	8
Comparator	5	16	31
Total	**10**	**39**	**26**

TABLE 3.

Clear and Almost Clear Score IGA Percentage of Enrolled Subjects			
Product	**# of 'Clear' and 'Almost Clear' Subjects (IGA=0 and IGA=1) following 4 weeks of treatment**	**Total # of Subjects who concluded the study**	**Percentage of 'Clear' and 'Almost Clear' out of 'Total' (%) Per examined product**
Kamedis Eczema Therapy Cream	6	10	60
Vehicle	5	13	38
Comparator	7	16	44
Total	**18**	**39**	**46**

calculated out of the total subjects for each treatment group (Table 2). The accumulated number of subjects reaching 'clear' and 'almost clear' or '0' and '1' score evaluations, respectively, were counted per each group and the percentage was calculated out of the total subjects for each treatment group (Table 3). The BSA was calculated by the sum of all specific body areas affected percentages from the total body surface affected percentage (Figure 4). The SCORAD was calculated according to the SCORAD equation presented at the introduction and took into consideration the extent and intensity as well as the subject's VAS parameters (Figure 5). The EASI was calculated using the extent of the representative body parts according to the EASI equation presented at the introduction (Figure 6).

The IGA severity scale was determined by counting all subjects that reached the 'clear' or '0' evaluation index with the percentage among the total number of the subjects. The test product reached 40% of the subjects reached an IGA rating of 'clear' while 31% of subjects using the comparator reached 'clear' and 8% of those using the vehicle (Table 2). Table 3 examined the number of patients that reached both 'clear' and 'almost clear' IGA scale parameters following the 4 weeks of treatment out of the total enrolled subjects within each treatment. The test product showed a percentage of 60% of 'clear' and 'almost clear' following 4 weeks of treatment. The comparator and vehicle showed 44% and 38%, respectively. Both IGA score analyses showed the advantage of the botanicals in the treatment of AD.

The BSA raw data is a decreasing percentage over time per each of the treatments (Figure 1). The improvement analysis of the BSA percentage is presented (Figure 2). The total BSA improvement percentage of the enrolled subjects per each treatment was standardized to the BL in order to enable a comparison be-

FIGURE 5. EASI raw data calculated per each visit in weeks duration.

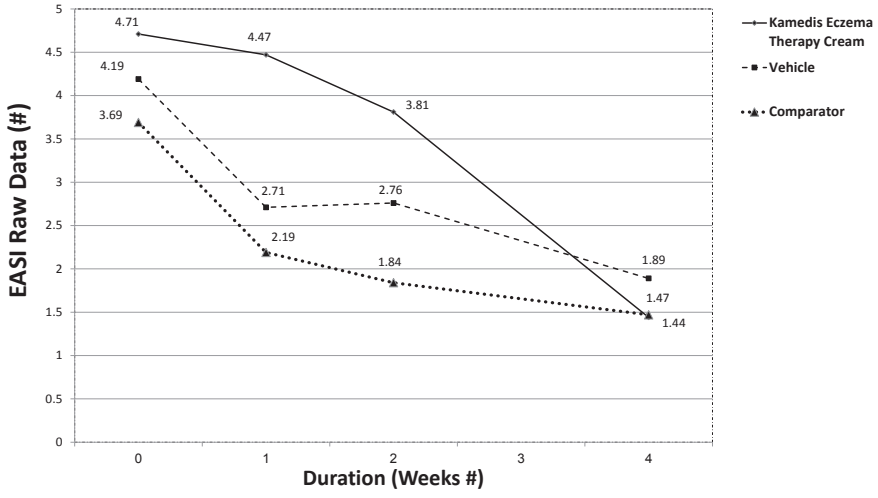
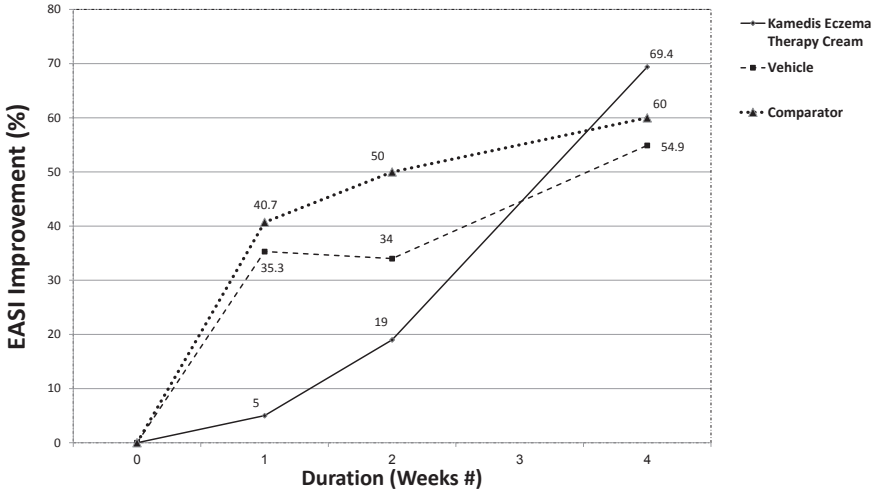


FIGURE 6. EASI improvement per each visit in weeks duration.



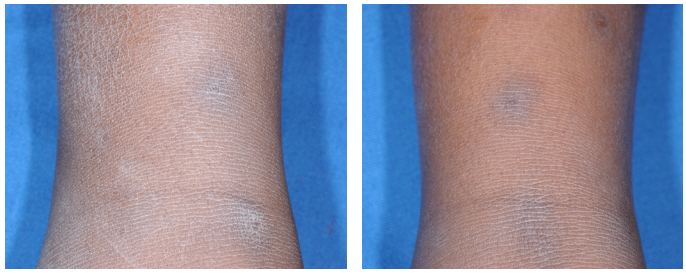
tween the alternative treatments. The severity of the subjects for the test product was higher in BL compared to the other two treatments: 14.58% BL severity within the children population versus 9.59% and 9.12% for the vehicle and the comparator, respectively (see Figure 1). The BSA for the test product improved more than the vehicle at every visit across treatment time, proving that the botanical test product is much more effective and beneficial than the vehicle. On day 28 the improvement of BSA for the test product reached 11% versus 4.63% with the vehicle treatment, yielding a 58% difference of improvement (see Figure 2). The test product showed an advantage over the comparator on day 14 and the end of the treatment on day 28. The test product achieved 5.33% improvement on day 14 and 11% on day 28 versus 2.72% on day 14 and 4.96% on day 28 for the comparator, demonstrating a difference of improvement change of 49% on day 14 and 55% on day 28. On day 7 the comparator showed an advantage over the test product, 2.43% of improvement versus no improvement of the test product. This preliminary trend changed by day 14 with the test product showing an advantage until the end of the treatment (see Figure 2). A comparison between the test product and the vehicle BSA improvement yielded a *P* value of less than 0.05, which is statistically significant, validating that the botanical combination is the factor responsible for the efficacy and improvement of the AD symptoms within this study population.

The SCORAD and EASI decreasing calculated index (Figure 3 and Figure 5, respectively) and the SCORAD improvement as well as the EASI improvement (Figure 4 and Figure 6, respectively) present similar trends. Following the treatment period, the test product showed 61.11% SCORAD improvement, the vehicle 56.6% and the comparator 52.9% (Figure 4). The comparator showed faster and better efficacy during the first 2 visits (day 7 and day 14), however did not sustain its improvement rise and ended up at day 28 less efficacious than the test product and the vehicle. The test product was 7.3% better than the vehicle and 13.4% better than the comparator. The EASI for the test product improvement of 69.4% following 4 weeks of the treatment, the comparator 60% and the vehicle 54.9% (Figure 6). The performance of the test product was better than the comparator by 13.5% and better than the vehicle by 20.9%. Both SCORAD and the EASI improvements did not reach statistical significance when taking into consideration the three treatment groups.

In addition to the measured and calculated parameters, clear improvement was visually evident as presented in the picture of this 10-year-old child before and after 4 treatment weeks of the test product (Figure 7a and 7b).

FIGURE 7. Visual improvement after 28 days (A): before treatment on day 0 (B): following treatment on day 28. 10-year-old girl.

(A) (B)



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DISCUSSION

This study confirmed and validated the efficacy of the botanical combination for the treatment of AD in children. The product containing botanicals significantly leveraged the healing process during the study duration. This advantage was validated in the analysis of IGA evaluation, BSA, SCORAD, and EASI improvement when compared to the results achieved by the vehicle and the comparator.

The botanicals are the major novelty of the test product with a 6% combination of ingredients with anti-inflammatory, antibacterial, and anti-oxidative activity (Table 4), which may assist in relieving the severity of eczema lesions. These herbs were chosen out of hundreds of other botanicals from a comprehensive literature review followed by in vitro studies on an artificial skin model.

For the purpose of evaluating efficacy of these botanicals during the course of the AD treatment, a vehicle product was developed to include the same ingredients in the same ratio as in the test product with the exception of the botanicals.

The test product was found to be much more effective in improving the AD severity and symptoms in this population of children compared to the vehicle at the end of the study duration. This result was validated by all investigated and calculated parameters: IGA index, BSA improvement, SCORAD, and EASI calculated indexes. The IGA for clear subjects was 40% for the test product compared to 8% for the vehicle (a difference of 80%), whereas the clear and almost clear IGA was 60% for the test product compared to 38% with the vehicle (a difference of 37%). The BSA improvement after 4 weeks was 11% with the test product and 4.63% with the vehicle (a difference of 58%). The SCORAD showed 61.11% improvement with the test product and 52.9% for the vehicle (a 13.4% difference). The EASI improvement kept the same trend of 69.4% improvement with the test product compared to 54.9% for the vehicle (a difference of 20.1%) supporting the higher efficacy of the test product with the botanicals. The botanicals demonstrated clinically and statistically superior results over the vehicle, especially from weeks 2 to week 4.

The comparator was added to the study in order to compare the effect of an OTC leading product in the US using colloidal oatmeal for the treatment of AD. It could be easily seen that the comparator was found to be better than the vehicle in majority of the evaluated and calculated parameters, however, less effective than the test product. The IGA for clear subjects was 40% for the test product compared to 31% with the comparator, (a difference of 22.5%), whereas the clear and almost clear IGA is 60% for the test product compared to 44% with the comparator (a difference of 27%). The BSA improvement after 4 weeks was 11% with the test product and 4.96% with the comparator (a difference of 55%). The SCORAD showed 61.11% improvement with the test product and 56.6% for the comparator (a difference of 7.4%). The EASI improvement revealed the same trend of 69.4% improvement with the test product compared to 60% for the comparator (a difference of 14%), supporting the higher efficacy of the test product with the botanicals.

TABLE 4.

Botanicals Characteristics	
Botanical Name	**Characteristic**
Rheum palmatum	Anti-inflammatory Anti-bacterial Anti-oxidative
Sanguisorba officinalis	Anti-inflammatory Anti-bacterial
Ailanthus altissima	Anti-inflammatory Anti-bacterial
Scutellaria baicalensis	Anti-inflammatory Anti-bacterial Anti-oxidative
Cnidium monnieri	Anti-inflammatory Anti-bacterial
Glycyrrhiza glabra	Anti-inflammatory Anti-bacterial

Over the years, numerous randomized double-blind studies[18-20] of topical botanical treatments for AD were published. In some of them, a vehicle was used while in others a comparator product. This was a vigorous study with a vehicle arm as well as a comparator arm. As we know, it is difficult to show superiority of the test product with botanical extract to an emollient vehicle, which we accomplished in this study.

DISCLOSURES

Dr. Draelos received funding from Kamedis to perform the research detailed in the manuscript. Dr Traub serves on the Medical Advisory Board for Kamedis and performed clinical research for this project. Dr. Gold performed clinical research for Kamedis Skin Care. Dr. Green performed clinical research for and serve on an advisory board for Kamedis. Dr. Amster has performed clinical research and received honorarium from Kamedis, Novartis, Leo, Valeant, UCB, Allergan, Botanix, Biopharmx, Foamix, Menlo, and Nielsen Biosciences. Deganit Barak-Shinar PhD is an employee of Kamedis Ltd., the sponsor of the study and manufacturer of Kamedis Eczema Therapy Cream. Dr. Kircik is an advisor, consultant, and an investigator for Kamedis.

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