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Validation of Botanical Treatment Efficiency for Adults and Children Suffering from Mild to Moderate Atopic Dermatitis

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ABSTRACT

Objective: The study was conducted to determine the efficiency of the botanicals combination incorporated in the Kamedis Eczema Therapy Cream (the tested product) for adults and children suffering from mild to moderate Atopic Dermatitis.
Design: The study designed as an interventional, multi-center, double-blind, randomized, controlled study.
Setting: Subjects were evenly randomly divided into three treatment groups: tested product, vehicle, and comparator. The vehicle used was the identical tested product without the botanical combination while the comparator was a leading OTC brand in the US market. All three above groups used a similar Kamedis wash for the body and face following by one of the three randomized treatment creams for the affected areas on the face and body.
Participants: One hundred and eight (108) subjects with uncomplicated, stable, mild to moderate atopic dermatitis recruited and qualified for the study; 71 females and 37 males, age 3 to 73.
Measurements: The investigator assessed the severity of each subject using the Investigator Global Assessment (IGA) and affected body surface area (BSA) at each of the visit days 0, 7, 14, and 28.
Results: The tested product demonstrated an improvement in IGA and BSA over the vehicle at every visit across treatment time, proving the validation that the botanical product is much more effective and beneficial than the same product without the botanicals. The tested product as well as the comparator reached exactly the same percentage, 34%, of 'clear' IGA subjects of the enrolled subjects, presenting advantage over the vehicle. The BSA improvement comparison analysis of the tested product over the vehicle yielded statistically significant *P* value of 0.0369.
Conclusion: The study results approve and validate that the botanical combination is the key factor for the efficacy and improvement of the AD symptoms within this study population.

J Drugs Dermatol. 2019;18(6):557-561.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease with a lifetime prevalence of 10-20% in children and 1-3% in adults.[1] AD usually starts in early infancy and is typified by pruritus, erythematous papulovesicular lesions, xerosis (dry skin), and lichenification of the skin.[2] In severe cases, intense pruritus (itching) and scratching may lead to secondary infection.[1] AD is usually associated with other atopic diseases as asthma and other allergic reactions.

Without an understanding of the complex and multifactorial pathogenesis of AD, treatment can be difficult and often unsatisfactory. When the structural integrity of the outer skin layer 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, and create chronic inflammation.[3-5]

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 immunosupressive

agents such as methotrexate, cyclosporin, and azathioprine. Due to their potential side effects, the last-mentioned treatments are not recommended for long-term use, especially in young children.[6-11]

Kamedis Eczema Therapy Cream (the tested product) is a barrier-based non-steroidal homeopathic formula 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 acts by adhering to the injured tissue, eliminating exogenous and contaminated factors related to dermatitis, protecting the skin from further irritation, and maintaining a moist skin environment.

Kamedis Eczema Therapy Cream developed to include a combination of six botanicals: Rheum Palmatum, Sanguisorba Officinalis, Ailanthus Altissima, Scutellaria Baicalensis, Cnidium Monnieri, and Glycyrrhiza Glabra with diluted sulphur. The botanicals are known from the literature to have significant anti-inflammatory and anti- allergic activities that assist in the relief of AD symptoms.[12-13] The purpose of this research was to validate the effectiveness of the botanicals for the treatment of AD. In order to meet this goal, a vehicle product formula was developed to be verified in comparison with the tested product. The vehicle product was designed to include all ingredients in the same relevant percentages as in the tested product without the combination of the six mentioned botanicals.

The analytical evaluation in this research was performed by using both Investigator Global Assessment (IGA) scale and the body surface area (BSA) for AD. The IGA score is based on the severity of erythema, infiltration, population, 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.[14]

METHODS

One hundred and eight (108) subjects with uncomplicated, stable, mild to moderate atopic dermatitis were recruited and qualified for the study, 71 female and 37 male, ages 3 to 73.

The study was designed as an interventional, multi-center, double-blind, randomized, controlled study. The study was conducted under Institutional Review Board (Integreview IRB, Austin, TX), a signed informed consent form and a photographic release form were obtained from each subject prior to performing any study procedure.

Subjects enrolled according to the inclusion criteria with 2 years of age and older, mild to moderate atopic dermatitis that meet the Hanifin and Rajka criteria and was stable for 7 days. Pregnant women 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 subject 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 extensively sun exposure during the study period.

In the study, subjects were evenly randomly divided into three treatment groups, 36 subjects in total were enrolled for each of the following treatment groups: tested product, vehicle, and comparator. The vehicle used was the tested product without the botanical combination and the comparator was a leading OTC brand in the US market. All three above groups used a similar Kamedis wash for the body and face and one of the three randomized treatment creams for the affected areas on the face and body.

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 (4 weeks), with study visits occurring at baseline (day 0), day7, day 14 and day 28. Subjects underwent facial and body investigator evaluation and AD lesion assessment by dermatologist at each of the visit days. Digital photos were taken of the affected lesions at each visit in one of the study's sites (33 subjects) by 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.

The investigator assessed the severity of each subject using Investigator Global Assessment (IGA) and affected Body Surface Area (BSA) at each of the visit days 0, 7, 14 and 28. The BSA was estimated by assessing the affected percentage of the following body areas: head, trunk, upper limbs and lower limbs for children and adults. For mild to moderate AD, the diagnosed BSA is typically lower than 10%.

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. During and following the treatment, on days 0, 7, 14, and 28, the subjects completed Dermatology Life Quality Index (DLQI) and by the end of the treatment, on day 28, a sponsor supplied marketing questionnaire, which also provided their comments for the entire experience.

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 significant interaction would mean that the difference between the treatment and the control is not similar across visits. Factors with *P* values smaller than 0.05 are considered as statistically significant. For each parameter, the original scores have been transformed to percentage of improvement by calculating the percentage of increased score comparing to the score measurement of each patient at baseline (day 0).

RESULTS

Of 108 subjects enrolled, 99 subjects completed the study. Nine subjects did not complete the study following the base line (BL) visit due to personal reasons that are not connected to the study. No adverse experiences or events occurred during the course of the trial.

Demographic characteristics of the subjects are presented (Table 1). No significant statistical difference was observed in IGA and BSA characteristics between each of the randomly selected treatments groups in the BL visit (day 0), however, a slight trend of more severe subjects was included in the tested product group comparing to the other two groups (Figure 1).

At each visit, the investigator assessed the subject IGA and BSA. The IGA is presented in severity index score evaluation. The number of subjects reached the 'clear' or '0' score evaluation was counted per each treatment and the clear percentage was calculated out of the total subjects successfully enrolled from for each treatment group (Table 2). The BSA is calculated by the relatively summation of all specific body areas affected percentages from the total body surface affected percentage (Figure 1).

The IGA severity scale parameter was examined by counting all subjects that reached the 'clear' or '0' evaluation index with the relatively percentage among the total number of the examined treatment product enrolled subjects. The tested product as well as the comparator reached exactly the same percentage, 34%, of 'clear' subjects out of the enrolled subjects (Table 2). Both the tested product and the comparator showed a higher percentage of 'clear' subject over the vehicle during the course of the study. The vehicle showed 19% only of 'clear' subjects from the total enrolled with this treatment. Again, showing the effectiveness or the benefit of the botanicals in the treatment of AD. Analysis of the accumulated number of 'clear' and 'almost clear' ('0' and '1' IGA evaluation scores) did not show any significant different between the three treatment products.

The BSA raw data is a decreasing total percentage over time per each of the treatments (Figure 1). The improvement analysis of the BSA total percentage is presented (Figure 2). The

TABLE 1.

Subject Demographic Characteristics	
Characteristic	**Value**
Age Range (years)	3-73 years old
Sex	Women - 71 (66%)
	Men - 37 (34%)
Race	African American - 58 (54%)
	Caucasian - 50 (46%)

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

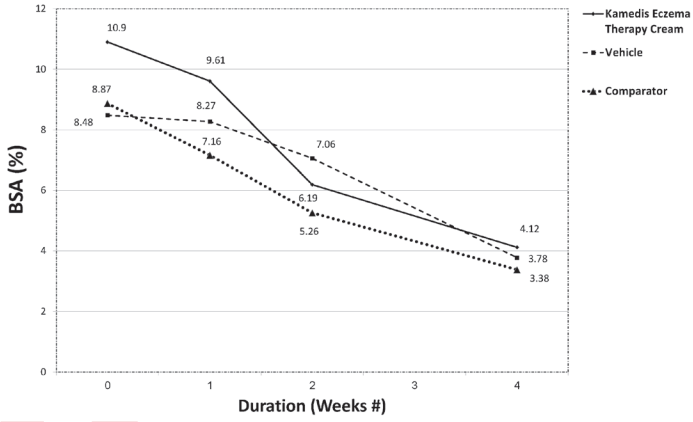
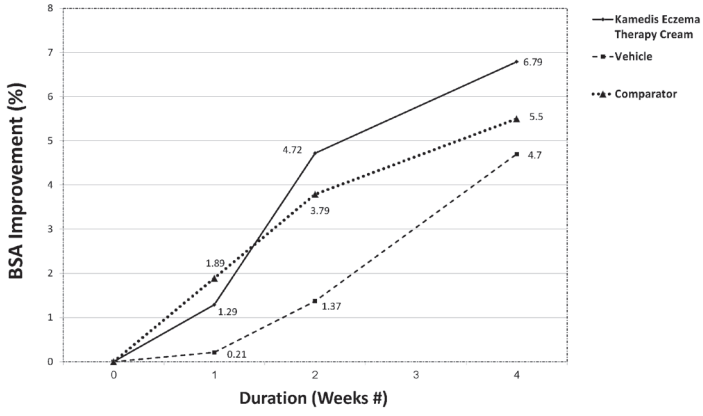


TABLE 2.

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	11	32	34
Vehicle	6	32	19
Comparator	12	35	34
Total	**29**	**99**	**29**

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



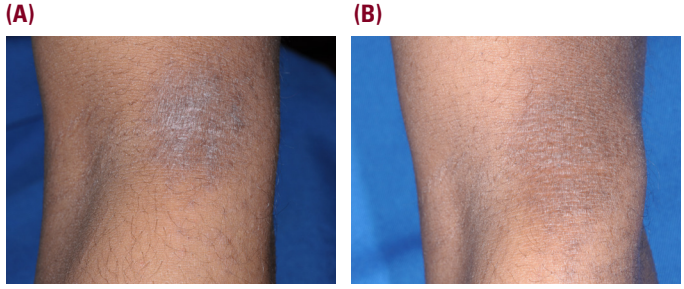
total BSA improvement percentage of the enrolled subjects per each treatment was standardized to the BL in order to enable a comparison between the alternative treatments. It should be mentioned that the severity of the enrolled subjects for the tested product was higher in BL comparing to the other two treatments, 10.9% of severity versus 8.48% and 8.87% for the vehicle and the comparator, respectively (see Figure 1). In general, it can be seen that the tested product demonstrated an improvement over the vehicle at every visit across treatment time, proving that the botanical product is much more effective and beneficial than the same product without the botanicals. On day 28 by the end of the treatment duration, the improved BSA with the tested product reached 6.79% versus 4.7% with the vehicle treatment. The tested product maintained its advantage over the vehicle during the course of all visits up to the final visit on day 28. An observed difference in the BSA improvement over the vehicle was achieved after one week (day 7) of treatment (1.29% vs 0.21%) and continued to expand over the vehicle after the following week (day 14) with 4.72% versus 1.37% until reached the final improvement detected after a month of treatment (day 28). The tested product showed an advantage over the comparator on week 2 (day 14) and the end of the treatment on week 4 (day 28). The tested product achieved 4.72% improvement on week 2 and 6.79% on week 4 versus 3.79% on week 2 and 5.5% on week 4 for the comparator. On week 1 (day 7), the comparator showed an advantage over the tested product, 1.89% of improvement versus 1.29% of the tested product. This preliminary trend changed over time keeping the tested product advantage until the end of the treatment. A comparison between the tested product and the vehicle BSA improvement yielded *P* value of 0.0369, which is statistically significant, therefore validates the botanical combination is a factor in efficacy and improvement of AD symptoms within this study population. *P* value of 0.0655 was achieved on week 4 for the tested product compared to both the vehicle and comparator alternative treatments.

In addition to the measured and calculated parameters, clear improvement was visually evident following 4 treatment weeks of the tested product (Figure 3a and 3b).

DISCUSSION

The main purpose of the presented study was to evaluate the efficacy of the botanicals that are the major novelty of the tested product for the treatment of AD. The tested product is based on 6% herbal botanical ingredients with anti-inflammatory and anti-bacterial activity such as the Rheum Palmatum, Sanguisorba Officinalis, Ailanthus Altissima, Scutellaria Baicalensis, Cnidium Monnieri, and Glycyrrhiza Glabra. The Rheum Palmatum and Scutellaria baicalensis also show anti-oxidative activity, which may assist in improving and relieving the severity of eczema lesions. The botanicals were selected due to their characteristics and were chosen out of hundreds of botanicals due to thorough literature review that was followed by in vitro studies on artificial skin model.

FIGURE 3. Visual improvement after 28 days (A) before treatment on day 0 (B) following treatment on day 28.



In order to examine the option of leveraging the treatment by the usage of the botanicals, a vehicle product was developed. The vehicle product was designed to include all ingredients in the same ratio as in the tested product excluding the botanicals. The tested product was found to be much more effective and very valuable in improving the AD severity and evaluated symptoms compared to the vehicle at every evaluated visit until the end of the treatment. The result was validated by both IGA index and BSA improvement calculation for the entire population that was tested in this multi-center study. This means that the botanicals demonstrated better results over time, especially between 2 to 4 weeks, in which the results become more visible and can be easily evaluated. The BSA improvement following the 4 weeks of treatment was increased by more than 40% from 4.7% to 6.79% and the IGA by more than 80% from 19% of clear subjects with the vehicle to 34% with the tested product.

The comparator was added to the study in order to examine the comparative 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 much better than the vehicle, however less effective than the tested product. The IGA analysis of the comparator showed similar results to the tested product with an advantage comparing to the vehicle results. The BSA improvement analysis of the comparator changed its trend after the first week of treatment. Once the first week of treatment showed an early improvement with the comparator with regards to the tested product, the following visits at 2 weeks and 4 weeks showed a different trend. While the comparator kept increasing its improvement, the tested product improved more and showed better effectivity in terms of BSA improvement percentages.

Over the years, numerous randomized double-blinded studies[15-17] were presented and published. In some of them, a vehicle was used for comparison purposes, while in others a comparator product was used. None of these studies used the

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vehicle tested formula in order to validate the efficacy of the exclusively botanicals combination that is the major and most important component of the final formula. This is the innovatively approach and the advantage of this study. While the vehicle emollient yielded good results in terms of skin barrier, the tested product usage managed to present statistically significant validation effect of the botanical complex incorporation.

DISCLOSURE

Z.D. Draelos received a research grant from Kamedis to conduct the research presented. M. Traub serves on the Medical Advisory Board for Kamedis and performed clinical research for this project. M.H. Gold performed clinical research for this project. L.J. Green is on the medical advisory board for Kamedis and was a principal investigator in this study. M. Amster has done clinical research functioning as the PI and been compensated by Kamedis, Novartis, Leo, Valeant, UCB, Allergan, Botanix, Biopharmx, Foamix Menlo, and Nielsen Biosciences. D. Barak-Shinar is an employee of Kamedis Ltd, the manufacturer of the Kamedis Eczema Therapy Cream as well as the sponsor of this study. L.H. Kircik has served as an investigator, advisory board member, and consultant for Kamedis. *Financial Support:* This study was wholly funded by Kamedis Ltd.

ACKNOWLEDGMENT

The authors would like to thank Oren Bar-Ilan and Nataly Livshits for their great contribution to the process with their vast support in the statistical analysis and data management.

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