



A Clinical Trial with Atopis™ Cream for the Treatment of Mild to Moderate Eczema

Iona E. Weir¹, Jhanna Molina², Simon Carson³

¹ Decima Health Ltd, Christchurch, New Zealand

² National Institute of Molecular Biology and Biotechnology, University of the Philippines, Diliman

³ Southern Clinical Trials Group, Christchurch, New Zealand

Correspondence to

Iona E. Weir

Email:

iona@decima.co.nz

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Abstract

BACKGROUND: Eczema is a common, chronic inflammatory skin disease characterized by itchy red rashes and scaly skin that can significantly affect the quality of life of patients. Moisturizing creams and emollients are often used to combat dryness and inflammation. The aim of this study was to demonstrate the efficacy of a topical study product in reducing the appearance and symptoms of eczema.

OBJECTIVE: We performed an open-label, adaptive-design, pilot study evaluating the efficacy of the Atopis™ product in reducing the appearance of eczema lesions and reducing the symptoms of itching, scaling, and redness.

METHODS: Healthy subjects aged 18–75 years with mild to moderate eczema, which was determined at screening visit, were enrolled in the study. Subjects topically applied the Atopis™ study product twice daily on areas identified with skin lesions for 5 weeks. On a daily basis, subjects completed the Visual Analog Scale for eczema symptoms — itching, scaling, and redness. Dermatologic assessments for severity and size of lesions and Severity Scoring of Atopic Dermatitis (SCORAD) were also assessed by a practitioner in the clinic at days 0, 7, 15, 30.

RESULTS: Forty subjects were screened and a total of 20 subjects completed the study. VAS Symptom Score for Itching demonstrated statistically significant decreases from baseline to Weeks 2, 3, and 4 ($p=0.001$, $p=0.011$, $p=0.031$, respectively). In addition, VAS Symptom Score for Scaling demonstrated statistically significant reductions from baseline to Weeks 2, 3, 4 ($p=0.000$, $p=0.003$, $p=0.031$, respectively). VAS Symptom Score for Redness displayed statistically significant decreases from baseline to all time points ($p=0.005$, $p=0.001$, $p=0.043$, respectively). Dermatologic assessments including SCORAD Index demonstrated statistically significant reductions from baseline (20.61) to Day 30 (10.26) (49.11%; $p=0.04$). Subjective measures of quality of life assessed through DLQI showed a statistically significant reduction of 48.03% from baseline (7.60) to Day 30 (3.95) ($p=0.031$).

CONCLUSION: Topical application of Atopis™ study product for five weeks appears to be effective for treatment of mild to moderate eczema as it significantly reduced the appearance of lesions as well as symptoms associated including itching, scaling, and redness. The study product was safe and tolerable for twice a day application as no adverse events were reported.

SOURCE OF FUNDING: Decima Health Ltd., Rangiora, New Zealand

Keywords: Atopis, eczema, clinical.



Introduction

Eczema is an inflammatory skin disease characterized by itchy red rashes commonly found in the elbows or behind the knees. Eczema lesions may appear as collection of fluid in the skin (vesicles) or as gross thickening of the skin (lichenification) with redness. It is also associated with crusting, scaling, cracking, and swelling of the skin. Mild eczema does not typically require medical treatment. However, a more severe form of eczema that occurs in childhood or early adulthood, referred to as atopic eczema or atopic dermatitis (AD), requires medical attention.¹ Prevalence of atopic dermatitis can be up to 20% in children and 1–10% in adults living in industrialized countries.^{2,3} Eczema

greatly affects the patients' quality of life and in fact it accounts for the lowest subjective score of QOL when compared with other dermatological diseases. A child with eczema often experiences itch and sleep disturbances, ostracism by other children, the need for special clothing and bedding, avoidance of physical activities such as swimming and the need for frequent application of ointments.^{4,5} The cause of eczema is not yet fully elucidated; however genetics and allergic and non-allergic factors seem to impact disease expression.⁴ In addition, abnormalities in the innate immune system, including defects physical barrier of the epidermis, alterations in microbial pattern recognition receptors, and a diminished capacity to increase the expression



of antimicrobial peptides during inflammation contribute to enhanced susceptibility to skin diseases. Antimicrobial peptides such as cathelicidin, HBD-2, and HBD-3 are often decreased in the skin of patients with atopic dermatitis compared to other inflammatory skin diseases.^{6,7} The Myriphytase™ extract has been developed to modulate the skin immune system by reducing allergenic responses and inflammation by regulating IL-10, IL-17 and TNF- α cytokine expression. Furthermore, the extract contains peptides, lipids and isomeric flavonoids which have antimicrobial, erythema, pruritus and wound healing properties. This extract is incorporated into a carrier cream Atopis™, which by comparing different formulations has been shown to synergistically enhance these properties whilst also, repairing the epidermis and provides a moisturizing physical barrier [unpub. data]. Eczema is commonly treated with antihistamine pills, creams or ointments. These control and alleviate itching and rash caused by severe eczema. It is also recommended that the skin be well lubricated to prevent it from becoming dry.¹ A systematic review of randomized clinical trials on atopic eczema summarized the interventions for treating the condition, which include pharmacological drug type (topical steroids), dietary interventions (dietary measures) or convenience (non-pharmacological treatments).⁴ The most common treatment for eczema are topical corticosteroids and these have been shown to improve various eczema dermatoses when topically applied.⁸

The Myriphytase™ extract is made using a patented enzymatic process combining components from the beehive (pollen, beeswax and honey) and raw coconut (oil and water) to produce an extract rich in fatty acids, vitamins, peptides, isomeric flavonoids and lipids. Atopis contains fatty acids such as lauric acid, myristic acid, linoleic acid, and alpha linoleic acid derived from pollen and the coconut. These fatty acids act in synergy with the isomeric flavonoids resulting in antioxidant, anti-microbial, anti-inflammatory and wound healing properties as determined by flow cytometric analysis of *in vitro* assays [unpub. data]. Included within this group of flavonoid constituents are catechins, quercetin, and isorhamnetin. These flavonoids have been previously shown to have anti-allergy, anti-inflammatory, antioxidant properties, as well as enhancing skin barrier function associated with eczema.⁹

The base cream Atopis™, has been designed to also include ingredients to work in synergy with the extract and which have been clinically shown to have efficacy in relieving the symptoms of eczema. Shea butter which contains antioxidants such as stearic acid, linoleic acid, and catechins¹⁰ is processed from the nut of the *Vitellaria paradoxa* (Shea tree). It is traditionally used as lotion for the skin and hair as it is considered an emollient and skin-conditioning agent.¹¹ Shea butter is also found in topical formulations used for inflammatory dermatoses such as psoriasis and atopic dermatitis.^{10,11} Shea butter consists of triterpene, cinnamates and cetates¹² and these were found to have anti-inflammatory activity, which can help in the reduction of edema associated with eczema. Human clinical studies have demonstrated shea butter as skin aging treatment, which regenerates skin and gives smoother, clearer skin.¹¹ Wrinkles from photoaging were also diminished. Another trial showed that shea butter has cicatrizing action in 70% of cases of hand dermatitis, sun burn and scars.¹¹ A cream with shea butter was also demonstrated to pro-

mote good moisturization of the skin compared to placebo.¹¹ Oil from *Macadamia integrifolia* nuts have been analyzed to contain catechol, phrogallol, and 3,4,5-trihydroxy phenolic compounds, known to function as antioxidants while the nut itself has also been cited as a good source of monounsaturated fatty acid, tocopherols, squalene and phytosterols, lipids that are known to lessen itch and inflammation of the skin.^{13,14} Vitamin E is known to decrease the serum levels of immunoglobulin E in atopic subjects. A single-blind clinical study reported remarkable improvements in facial erythema, lichenification, and the appearance of normal skin in subjects with eczematous lesions who were given 268 mg of vitamin E and these effects were mostly due to the decrease in pruritus.¹⁵ In another randomized, double-blinded, placebo-controlled trial with 45 eczema patients, SCORAD assessment (Severity Scoring of Atopic Dermatitis) showed improvement in the patients who ingested vitamin E supplements.¹⁶ This open-label, adaptive design study was undertaken to determine the efficacy of Atopis™, in the treatment of eczema assessed by subjective ratings of symptoms and dermatologic assessments.

Methods

Investigational Product

The investigational product for this study was Atopis™. It consists of a base cream with the following ingredients including cetearylolate and sorbitanolate, shea butter, macadamia nut oil, safflower oil, glycerine, geogard, and vitamin E. The extract Myriphytase™ comprises 10% of the final cream and contains proprietary lypolysed fatty acids, isomeric flavonoids, peptilipids, and peptides created by enzymatically reacting pollen, beeswax, honeydew, coconut oil and coconut water together which was then added into the base cream. The study product was provided by the sponsor and was GMP certified. It was applied twice a day on affected areas of the skin. Immunomodulators, immunosuppressants and oral as well as topical supplements were not allowed during the course of the study. Permitted medications included hormonal contraception, including oral, patch, or devices.

Subject Population

The study aimed to enroll healthy males and females with eczema symptoms between 18 and 75 years old and with a Body Mass Index between 20 and 35 kg/m². Subjects had a mild to moderate eczema which was determined at screening visit and agreed to use the study-supplied cleanser and moisturizer as the only body cosmetic applied to irritated skin and stop all medications and supplements during the entire length of the study. Subjects with clinically significant renal, hepatic, endocrine (including diabetes mellitus), cardiac, pulmonary, pancreatic, neurologic, hematologic, or biliary disorder were excluded from the study. Also not allowed were those with known allergy or sensitivity to herbal products as well as history or presence of cancer in the prior two years, including any skin cancer or suspicious lesions.

Study Design

This study was an open-label pilot study. Medicus Research LLC in Los Angeles, California was the contract research organization (CRO) for this study. Institutional review board (IRB) approval

Table 1. Demographic and Baseline Characteristics

Baseline Characteristics	MyriCell™ STUDY PRODUCT
<i>n</i> (Total number of randomized, inclusive of early terminated)	21
Male	7
Female	14
Age (Mean)	31.48
Age (Range)	31.48 ± 9.02
Weight (Mean)	154.69
Weight (Range)	154.69 ± 33.71
Height (Mean)	65.64
Height (Range)	65.64 ± 4.45
BMI (Mean)	25.26
BMI (Range)	25.26 ± 4.58
Marital Status	
Single	17
Married	2
Divorced	2
Ethnicity	
Latino/Hispanic	2
Asian	3
African-American	8
Caucasian	8

was received on December 5, 2013 by the MaGil IRB (Rockville, MD) prior to the initiation of any study-related activities. The trial concluded following enrollment and completion of the required number of subjects (June 14th, 2014).

An in-clinic screening visit was conducted seven days prior to the baseline visit. Subjects underwent the informed consent process and were screened in the presence of all inclusion criteria and the absence of all the exclusion criteria. The screening process also included gathering of demographic data, an interview on detailed medical history and medications, physical examination, assessment of the vital signs temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and weight as well as urine collection to run pregnancy tests for females of child bearing potential. This visit also included dermatologic assessments wherein dermatologic examinations were performed by a qualified practitioner. Assessment included the Severity Scoring of Atopic Dermatitis (SCORAD) an evaluation and grading of lesion quality. SCORAD is a clinical tool used to assess the extent and severity of eczema. Dermatologists may use this tool before and after treatment to determine whether the treatment has been effective from a clinical perspective.¹⁷ Subjects also completed the Dermatologic Life Quality Index (DLQI), which consists of 10 questions concerning the patients' perception of the impact of skin diseases on different aspects of their health related quality of life over the last week. Photographs of skin lesions were obtained and these were examined and identified by anatomical location and size. To determine a possible risk of allergenicity, at each visit the skin was examined for any indication of skin allergy such as hives, which were not present at the baseline visit.

Subjects underwent a 7-day washout period of any treatments for

eczema, and returned to the clinic at Day 0 (Baseline) for a review of intercurrent medical and concomitant medication history and assessment of vital signs. Dermatologic assessments were also conducted at this visit. Subjects were given one-week supply of the study product, the daily dosing diary, and the Dermatologic Life Quality Index (DLQI).

At Day 7, Day 15, and Day 30, subjects returned to the clinic for repeat assessments and for retrieval procedures. The study duration was up to 5 weeks.

Endpoints

The primary objective was to determine the efficacy of Atopic™ in the treatment of eczema. Endpoints included the following: Reduction of symptoms of itching, scaling, and redness measured by Visual Analog Scale, and Dermatologic Assessments including Dermatologic Examination Documentation Form for Severity and Size of Eczema, Severity Scoring of Atopic Dermatitis (SCORAD), and Dermatology Life Quality Index (DLQI). Severity of eczema was rated from being Mild to Severe. The secondary objective was to evaluate the safety of administration of 30 day dose of the Atopic™ study product through Adverse Event Analysis and Vital Signs.

Statistics

This study was designed as an adaptive clinical trial with interim analysis at 20 subjects, with the potential to recruit up to 50 subjects if required. Statistical significance was achieved at 20 subjects and thus recruitment was closed at 20 subjects. Parallel dual data entry was done by data management personnel across all endpoints. Data validation and reconciliation of parallel entry occurred after the dual data entry process. The monitoring team compared the values on the original CRFs or source documents, correcting any discrepancies found. All data elements were screened for reasonableness, and all missing, suspicious, or impossible values were referred back to the monitoring team for query generation and resolution. The database was formally locked after all suspicious entries in the database were resolved. Descriptive measures such as means, standard deviations, and standard errors of means were processed for each numeric endpoint (i.e. VAS for Symptoms of Itching, Scaling and Redness, SCORAD and DLQI) at all visits. Percentage changes were used to quantify the increase or decrease of endpoints from baseline. For each endpoint in ordinal scale, the differences in the medians within time periods for Atopic™ product was tested for nominal significance using non-parametric test (Wilcoxon Signed Rank Test or Sign Test). For each endpoint in the continuous scale and follows normal distribution (or have semblance to normality), difference from baseline to each subsequent time points for each product was tested for nominal significance using paired Student t-test. If the data was found to violate assumptions on normality, non-parametric Wilcoxon Signed Ranks test or Sign Test was used. A Modified per Protocol (Mod PP) analysis was performed to assess the efficacy variables of the study. Subjects with at least one post-dose Visit completed were included in the analysis. All efficacy endpoints were analyzed depending on the level of measurement of the endpoint. VAS, SCORAD and DLQI were assessed using Paired T-test or by the non-parametric Wilcoxon Signed Ranks test or Sign Test for those data that were found

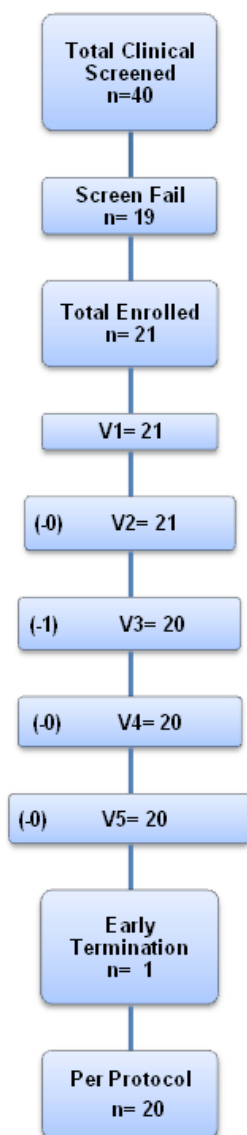


Figure 1. Attrition Chart.

to be substantially non-normally distributed. Ordinal scales like Dermatologic Examination Documentation Form were tested using non-parametric Sign test to assess if there was a significant difference on the distribution within times.

Continuous Endpoint like Vital Signs were tested for significant changes from Baseline to each subsequent time points for each product using Paired T-test or Wilcoxon Signed rank test or Sign test if data distribution found to be non-normal. To obtain comparable documentation on AEs, the investigator asked the subject the following open, standardized, questions at each visit. Frequency and intensity of AE's and serious AE's were recorded in detail, based on the subject's interviews during each visit. Recorded AE's were grouped by general type of event (body system). Differences in AE patterns of Atopis™ were assessed by McNemar Change Test.

All tests of hypotheses were done at alpha=0.05.

Results

Forty subjects were screened and 21 were enrolled in the study, with a total of 20 subjects completing the study and 1 drop out (Figure 1). The demographics and baseline characteristics are

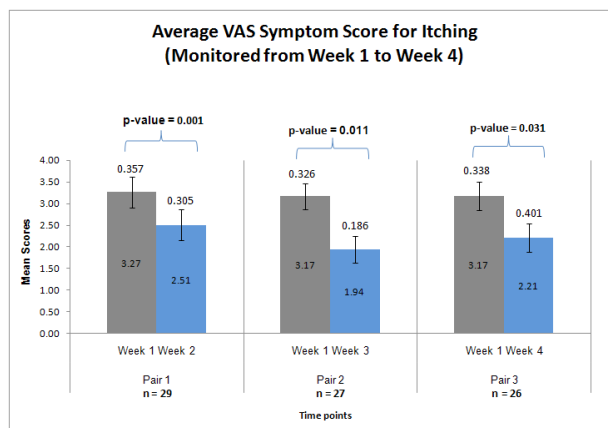


Figure 2. Comparison from Week 1 in Average VAS Symptom Score for Itching.

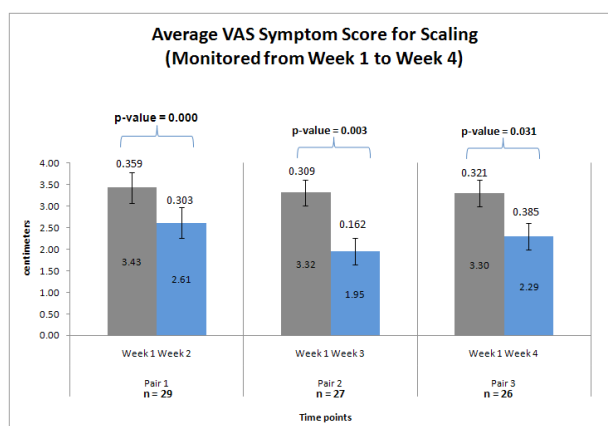


Figure 3. Comparison from Week 1 in Average VAS Symptom Score for Scaling.

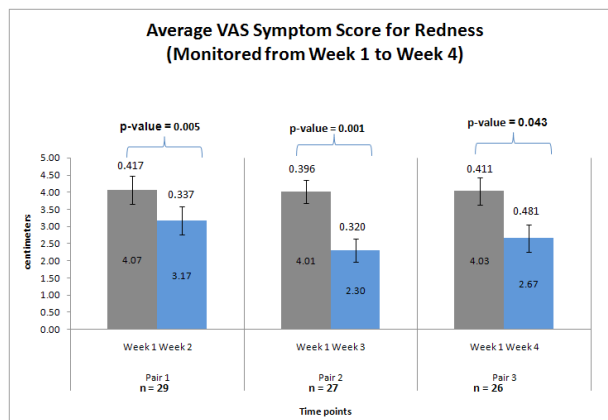


Figure 4. Comparison from Week 1 in Average VAS Symptom Score for Redness.

shown in Table 1.

The primary objective was to evaluate the efficacy of the Atopis™ study product in the treatment of eczema by measuring the reduction of appearance of lesions as well as the symptoms of itching, scaling, and redness. VAS Symptom Score for Itching demonstrated statistically significant decreases from baseline to Weeks 2, 3, and 4 (p=0.001, p=0.011, p=0.031, respectively). The greatest reduction of 38.73% was observed from baseline to Week 3. Similarly, VAS Symptom Score for Scaling demonstrated

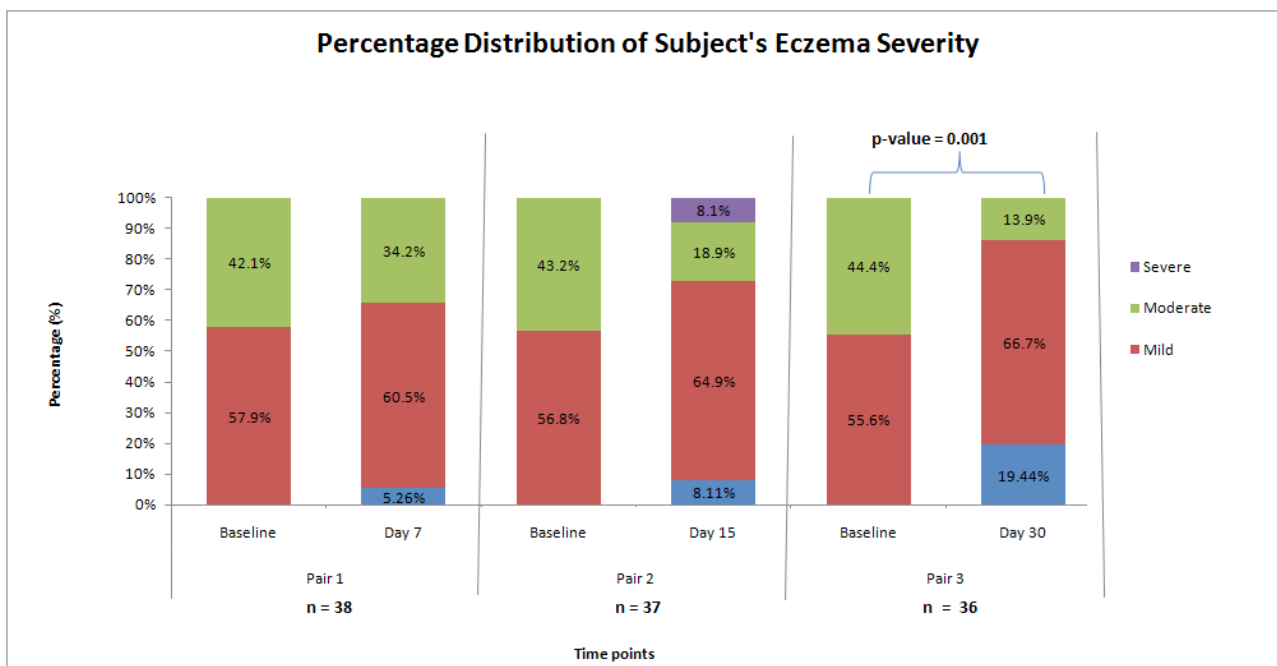


Figure 5. Comparison from Baseline in Percentage Distribution of Eczema Severity.

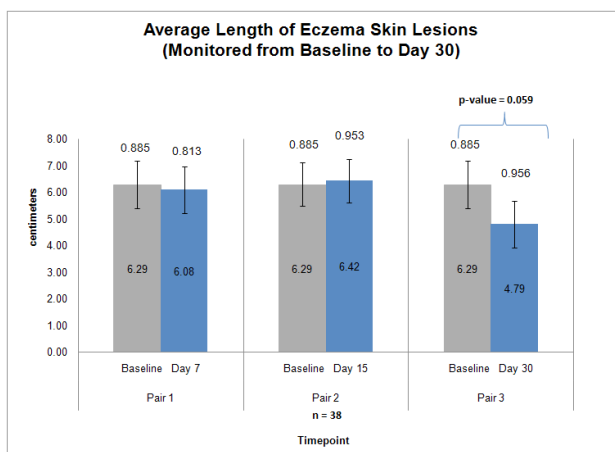


Figure 6. Comparison from Baseline in Average Length of Eczema Skin Lesions.

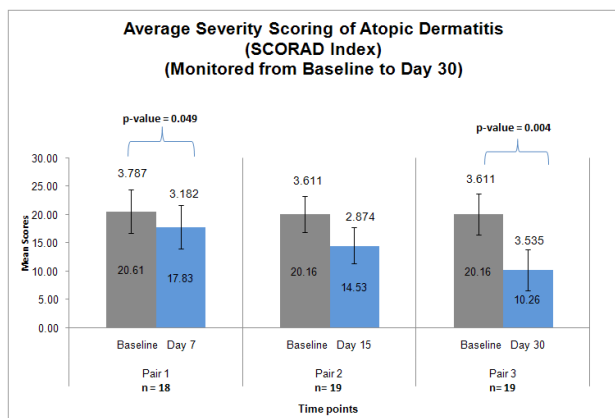


Figure 7. Comparison from Baseline in Average Severity Scoring of Atopic Dermatitis.

statistically significant reductions from baseline to Weeks 2, 3, 4 (p=0.000, p=0.003, p=0.031, respectively). The greatest decrease was also observed from baseline to Week 3 (-41.09). Lastly, VAS Symptom Score for Redness displayed statistically significant decreases from baseline to all time points (p=0.005, p=0.001, p=0.043, respectively). The greatest change from baseline of 42.68% was found from baseline to Week 3 (Figures 2-4).

Dermatologic Assessments included Dermatologic Examination Documentation Forms for Severity and Size, SCORAD and were measured by a dermatologist. DLQI was completed by the subjects. Eczema Severity rated from being Mild to Severe demonstrated statistically significant changes from baseline. In particular, 16 subjects (44.4%) who had Moderate Eczema from baseline was reduced to only 5 subjects (13.9%) by the end of the study period while 7 subjects (19.44%) had disappeared skin lesions after 30 days from 0% at baseline (Figure 5). The Average Length of Eczema Skin Lesions, measured in centimeters, displayed a nearly significant reduction from baseline (6.29 cm) to Day 30 (4.79 cm) (p=0.059), corresponding to a decrease of 1.5 centimeters by the end of the study (Figure 6). The Average Width of Eczema Skin Lesions did not demonstrate any statistically significant changes from baseline to any time point. SCORAD Index demonstrated statistically significant reductions from baseline (20.61) to Day 7 (17.83) (13.49%; p=0.049). By the end of the study, it statistically significantly decreased to 10.26 (49.11%; p=0.04) from baseline, corresponding to a 9.9 mean reduction (Figure 7). DLQI demonstrated a statistically significant reduction of 48.03% from baseline (7.60) to Day 30 (3.95) (p=0.031) (Figure 8).

No clinically significant changes were observed for the vital signs of temperature, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and weight. Lastly, there were no serious adverse events or non adverse events reported in the study.

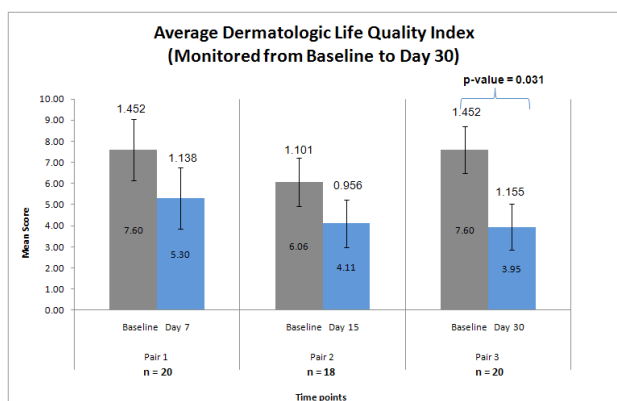


Figure 8. Comparison from Baseline in Average Dermatologic Life Quality Index.

Discussion

In this trial, the study product Atopis™ was assessed for its safety, allergenicity (as in was hives or skin allergies observed) and efficacy at reducing the severity of eczema symptoms in a population of subjects suffering from mild to moderate eczema. Severity was assessed using several standardized parameters, including the size and number of lesions as well as itching, scaling and redness symptoms. The results indicate that the application of study product twice a day for 4 weeks reduced the severity, average size of lesions and symptoms associated with eczema. Over the course of the 5 week study, no adverse events were reported, suggesting that daily application of the study product Atopis™ is safe and well-tolerated in patients suffering from mild to moderate eczema.

While eczema is not typically a life threatening condition, it severely impacts patient quality of life.^{4,5} One of the most unpleasant symptoms associated with eczema is itching, which has become the primary diagnostic criteria and hallmark of AD.¹⁸ In the present study, visual analog scale for itching demonstrated reduction from 3.27 to 1.94 after 3 weeks of twice a day application of Atopis™, although this score increased slightly at week 4. Relief of this symptom is clinically important as patients are known to scratch eczema until it bleeds, and suffer from psychological and sleep disturbances.¹⁹ Being such a prominent aspect of AD, itching should be managed as part of AD treatment. Doctors typically recommend eliminating factors that trigger itching and targeting inflammations with the use of medications.²⁰ The study product Atopis™ achieved significant itching relief in the absence of prescription medication.

Eczema progression is marked by the loss of epidermal lipid barrier integrity,^{21,22} which is physically manifested as the formation of scales. Maintenance of the skin barrier can be bolstered using emollients and some additives,²⁰ which decreases scaling symptoms. In the current study, scaling VAS symptoms were reduced from 3.43 to 1.95 after 3 weeks of Atopis™ application, and redness was reduced from 4.07 to 2.3. These results suggest that the study product Atopis™ is effective at helping to maintain epidermal integrity and reduce redness during an eczema outbreak. This is in line with previous observations that application of moisturizing creams to treat dry and scaly skin have a positive impact on quality of life among patients.^{23,24}

Rating of eczema size and severity were measured by a practitioner to produce standardized dermatologic assessments be-

tween visits. After 7 days of Atopis™ application, 2 of the 20 participants were completely cleared of lesions. This number increased by the end of the study period (Week 4) when lesions were found to be absent in 7 of the 20 participants. For the remaining lesions still observed at the end of the study, lesion severity shifted from moderate to mild in the majority of patients. As expected from these results, the objective measurement of skin lesion length also decreased by an average of 1.5 cm from baseline to the end of the 4 week period. SCORAD, another tool to assess severity of skin lesions, demonstrated a 9.9 point reduction from baseline by the end of the treatment period confirming the improvements in severity of the disease. Subjects' perception of the impact of skin diseases on different aspects of their health related quality of life was also found to reduce by 48% as assessed by DLQI.

Atopis™ treatment is expected to be superior to placebo treatments when we analyze historical data chronicling the usual course of an eczema outbreak. One large multicenter human trial performed by Eichenfield et al. collected detailed information on how participants fared when given a placebo to treat their AD as compared to a topical corticosteroid.¹⁷ The Eichenfield et al. study found that over the course of 43 days the 136 patients receiving placebo treatment maintained or increased eczema area and severity from their baseline measurements.¹⁷ Only 18.4% of the placebo group in the Eichenfield study cleared disease signs, which can be compared to the results of the current study where 35% clearance recorded after 4 weeks of Atopis™ application.²⁴ Although the study groups cannot be compared side-by-side (participants were recruited and assessed by slightly different parameters), the results suggest that the study product Atopis would improve eczema even when compared to placebo treatment.

This outcome is not unexpected as the study product Atopis™ base cream is formulated with the various ingredients Olivem1000, organic shea butter, organic macadamia nut oil, organic safflower oil, glycerin, geogard, and vitamin E which have been previously shown to possess anti-inflammatory, and emollient properties.¹² The extract has been developed using ingredients from the beehive (pollen, beeswax and honeydew) and coconuts which undergo an enzymatic fermentation process to produce, isomeric flavonoids, lypolysed fatty acids and peptides which have anti-redness, anti-itch and anti-scaling properties.

Remarkably, treatment with Atopis™ did not yield any adverse events, suggesting a very low allergenicity and high safety for patients suffering from AD. Because AD sufferers are characterized by very sensitive skin, this rate of adverse events is quite low when compared to historical clinical trial outcomes gathered from various standard-of-care treatments. A systemic review of clinical trials that studied emollients for AD/eczema treatment reported adverse events categorized as "burning sensations" in four of the seven studies evaluated.⁴ One trial that evaluated a fluticasone propionate corticosteroid cream, commonly prescribed for AD treatment, found that the product resulted in adverse events in 91 out of 270 patients. These events included exacerbation of eczema, skin irritation and itching.²⁵ In those patients who are able to tolerate topical corticosteroid treatment, it is still recommended that therapy be limited to a maximum of 3 weeks to minimize skin-thinning side effects.²⁶ The results gathered from the current study suggest that Atopis™ may be less

irritating and produce fewer side-effects than some standard-of-care medications.

Although there are no previous human clinical studies using the similar formulation relating to eczema or atopic dermatitis, it appears that the combined effects of the components may be effective and safe in the treatment of eczema using study product Atopis™. This study demonstrated for the first time the efficacy of a proprietary blend of natural ingredients which have emollient and anti-inflammatory properties in reducing the appearance of eczema lesions and associated symptoms of itching, scaling, and redness. Larger randomized, placebo-controlled clinical studies are required to confirm these preliminary findings.

Topical application of Atopis™ study product for four weeks appears to be effective for treatment of mild to moderate eczema as it significantly reduced the appearance of lesions as well as symptoms associated including itching, scaling, and redness. The study product was safe and tolerable for twice a day application as no adverse events were reported.

Competing Interests

Dr Weir is a shareholder and director of Decima Health Ltd. Southern Clinical Trials Group are clinical site providers for another clinical trial for Decima Health Ltd.

Authors' Contributions

IEW was the inventor of the Atopis cream and Myriphytase extract, and contributed to the writing of this manuscript and the protocol design. JPLM (formerly of Medicus Research LLC), contributed to the writing, data analyses, and data interpretation that are part of this manuscript. SC provided clinical review and advice.

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