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Evaluation of the Efficacy of IALUSET VITAL® Cream in Helping the Improvement of the Atopic Dermatitis Symptoms in Adults: A Randomized, Double Blind, Vehicle-Controlled Clinical Trial

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Abstract: Atopic dermatitis (AD) is a chronic relapsing skin disease, associated with impaired skin barrier function and characterized by poorly defined pruritic, erythematous lesions. In this study, the efficacy of a new topical cream (IALUSET VITAL®), containing hyaluronic acid and the extract of *Salvia haenkei*, in reducing symptoms of moderate AD in adults was investigated. This study was a randomized, double blind, vehicle-controlled clinical study. Treatment efficacy was evaluated considering both objective parameters (Scoring Atopic Dermatitis, SCORAD) and subjective parameters (Patient Oriented Eczema Measure, POEM, and an itching sensation) and through non-invasive bioengineering techniques to measure skin moisturization and Trans Epidermal Water Loss (TEWL). Under the experimental conditions of the study, IALUSET VITAL® significantly reduced AD severity, as shown by the SCORAD index, and was revealed to be effective in alleviating the most common signs and symptoms of moderate AD, suppressing itch and improving skin moisturization, and to have a good safety profile, being well-tolerated by patients. However, statistically significant differences between active and vehicle group were not found in the other parameters analyzed, likely because the basic formulation of IALUSET VITAL® guarantees good emollient properties and the addition of hyaluronic acid and extract of *Salvia haenkei* as active ingredients results in a great increase in effectiveness.

Keywords: atopic dermatitis; hyaluronic acid; *Salvia haenkei*; clinical trial; cream; SCORAD

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1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting up to 20% of children and up to 3% of adults [1], characterized by erythematous skin lesions with intense pruritus, a very disabling symptom that considerably impairs a patient's quality of life. It is widely recognized that AD is a multifactorial disease, involving immune disorders, impaired skin barrier function and environmental factors. Nevertheless, a major debate exists as to whether AD is primarily driven by immune dysregulation (inside-out theory) or epidermal barrier dysfunction (outside-in theory) [2,3]. Common tracts of 10–40% of AD patients are the loss-of-function mutation of the *FLG* gene, encoding the structural epidermal protein filaggrin, contributing to epidermal barrier dysfunction [4,5] and a reduced content of ceramides, important water-holding molecules in the extracellular space in the horny layer [6]. These events lead to trans-epidermal water loss, a component of a physiological process known as *perspiratio insensibilis*, and increased permeability to allergens and pathogens and promotes inflammation stimulating the activation of the innate immune response. Cutaneous sensory nerves transmit the increased itch signal

to the brain, which leads to further scratching and impairing of skin integrity with the establishment of a self-feeding vicious circle [2,7]. With regard to the treatment of AD, current therapies aim to clear inflamed lesions and reduce itch in order to improve patient's everyday life. Topical therapies with emollients and anti-inflammatory drugs are the mainstay for mild-to-moderate AD; phototherapy and systemic immunomodulatory drugs can be effective in more-severe AD [8].

Hyaluronic acid (HA), a polysaccharide composed of alternating glucuronic acid and N-acetylglucosamine residues, is one of the main components of the extracellular matrix [9], especially in the skin that accounts for about 50% of the total content of HA in the body [10]. HA is a key factor in wound healing and tissue repair processes, being involved in proliferation, differentiation, and migration of keratinocytes [11–13], as well as in skin aging owing to its ability to retain water and moisturize skin [9]. In addition, evidence from animal studies have shown that HA is also involved in the establishment and homeostasis of epidermal skin barrier, regulating both epidermal differentiation and lipid synthesis/secretion through the interaction with its receptor CD44 [13,14]. In addition, clinical studies support the safety and the efficacy of hyaluronic acid-based emollient foam in treating patients with moderate AD [15,16].

Herbal extracts have been used for the treatment of skin diseases, among which AD, for centuries [17]. Recently, both in vitro and clinical studies have shown the efficacy of the extract of *Salvia haenkei*, a plant native of Bolivia largely used in traditional medicine [18], as an anti-aging agent [19,20]. In addition, an extract of *Salvia haenkei* has been patented both as re-epithelizing and cicatrizing agent [21] and as an active agent in the treatment of dermatological diseases [22].

The aim of this study was to evaluate the efficacy of a novel topical cosmetic product, namely IALUSET VITAL®, composed of a mixture of HA molecules and the extract of *Salvia haenkei*, in the treatment of pruritus and skin dehydration in moderate AD.

2. Materials and Methods

2.1. Study Design

This study was a randomized, double blind, vehicle-controlled clinical study conducted at Complife Italia S.r.l., Garbagnate M.se (MI) Italy. All subjects enrolled gave written informed consent. All the study procedures were carried out in compliance with the ethical principles for medical research (Ethical Principles for Medical Research Involving Human Subjects, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and its amendment). The study received approval from the Ethics Committee for Non-Pharmacological Clinical Investigations and was registered in the ISRCTN registry (ISRCTN11607227; https://doi.org/10.1186/ISRCTN11607227, accessed on 11 April 2019).

2.2. Study Population, Randomization, and Treatment

The subjects participating in the study (n = 40) were screened starting from a database of 48 subjects and enrolled under the supervision of a board-certified dermatologist from a panel of healthy male and female subjects, of Caucasian ethnicity, aged between 18 and 65 years old (mean age: 42.5 years active group and 45.7 years vehicle group), showing moderate atopic dermatitis (SCORAD between 25 and 40) at baseline. Subjects having a positive history for hypersensitive skin, former history of allergy or sensitivity to cosmetics, toiletries, to solar and/or topical medications, and the history of any confounding inflammatory skin diseases or any other skin disease (e.g., psoriasis, rosacea, erythroderma or ichthyosis), with spontaneously improving or rapidly deteriorating AD, active allergic contact dermatitis, or other non-atopic forms of dermatitis, acute infections, any skin condition that the principal investigator deemed inappropriate for participation or that were pregnant or nursing women were excluded from participation in this study. The study further excluded subjects having (a) oral or intravenous corticosteroids, UVA/UVB therapy, PUVA (psoralen plus ultraviolet A) therapy, tanning booths, non-prescription UV light sources, immunomodulators or immunosuppressive therapies, interferon, or cyto-

toxic drugs, within four weeks before baseline, and (b) antihistamines, topical antibiotics, topical corticosteroids, topical calcineurin inhibitors, or other topical drug products used for treating AD, within one week before baseline.

After the enrollment, a restricted randomization list was generated using PASS 11 (version 11.0.10; PASS, LLC, Kaysville, UT, USA) statistical software running on Windows Server 2008 R2 Standard SP1 64-bit edition (Microsoft, Redmond, WA, USA). The list was created by a biostatistician and stored in a safe place. The randomization sequence was stratified using 'Efron's biased coin' algorithm with a 1:1 allocation ratio. Participants were randomized into two groups: the active group applied the IALUSET VITAL® cream and the control group applied the vehicle cream (Figure 1A). The study adhered to established procedures to maintain separation between the investigator and its collaborators and the staff that delivered the intervention. Investigator and its collaborators who obtained outcome measurements were not informed on the product group assignment. Staff who delivered the intervention did not take outcome measurements. Subjects, investigator, and collaborators were kept masked to products' assignment.

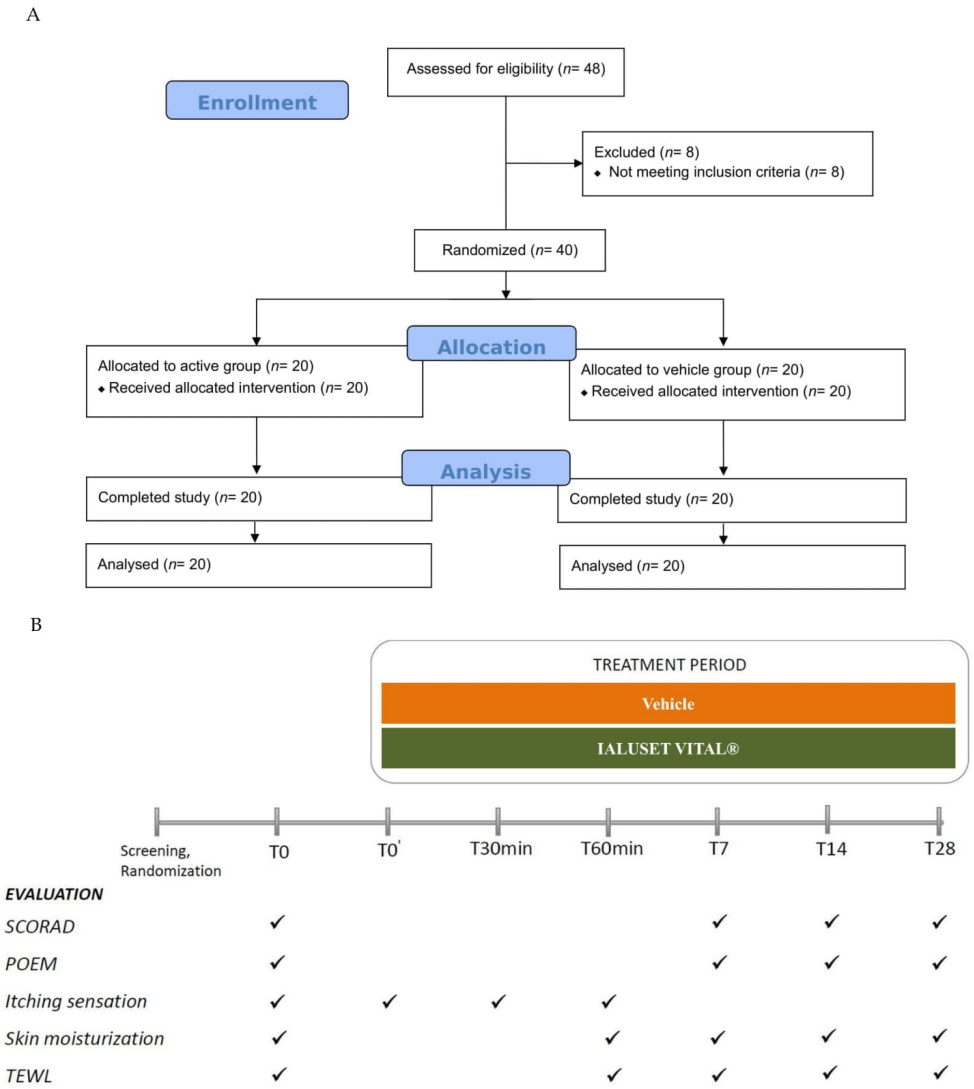

Figure 1. Study design. (**A**) participant flow chart; (**B**) evaluation of symptom severity in AD patients after treatment with vehicle vs. IALUSET VITAL®, through the parameters shown at the indicated time points.

The day before the baseline visit subjects were asked to abstain from any topical product (e.g., sunscreens, lotions, creams) application in the areas to be treated. Reference

and active products were applied on the area affected by atopic dermatitis twice a day or more, according to individual needs. Product efficacy was assessed immediately after the first product application (T0′), after 30 (T30min) and 60 (T60min) minutes and after 7 (T7), 14 (T14), and 28 (T28) days of use. Enrolled subjects were intended to use during the entire study period only the product to be tested and to not vary the normal daily routine (Figure 1B).

2.3. Study Outcomes

Severity of AD was evaluated by means of objective and subjective methods. Objective evaluation was performed by means of scoring atopic dermatitis index (SCORAD) [23]. Subjective evaluations were performed by means of the Patient Oriented Eczema Measure (POEM), a validated tool used for monitoring atopic eczema severity, focusing on the illness as experienced by the patient [24] and by means of an additional questionnaire about itching sensation with a score scale from 0 (no itching sensation) to 10 (very strong itching sensation). Efficacy of treatment was evaluated also through non-invasive bioengineering techniques. Skin moisturization was measured by means of Corneometer® equipment (Corneometer® CM 825; Courage + Khazaka, electronic GmbH, Köln, Germany), whereas a skin barrier function was evaluated by measuring Trans Epidermal Water Loss (TEWL) using a Tewameter® TM 300 (Courage + Khazaka, electronic GmbH, Köln, Germany).

2.4. Statistical Analysis and Interpretation of Results

The instrumental data were submitted to a two-way Student *t*-test while the clinical data were submitted to a Wilcoxon (intragroup comparison) or Mann–Whitney test (intergroup comparison) signed rank test for paired data. Intragroup (vs. T0) or intergroup (active vs. vehicle) variations were considered statistically significant when the *p*-value was <0.05. For clinical evaluations, the positive effect of the product on the measured parameter was confirmed if more than 50% of the subjects registered an improvement. Finally, for the self-assessment questionnaires, the performance and the pleasantness of the product must be perceived by at least 60% of the subjects.

2.5. Reference and Test Cream

The reference and test cosmetic products were in line with the Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) (Text with EEA relevance) and to its annexes. Test cream (IALUSET VITAL®, IBSA Farmaceutici Italia) contained a mixture of two different molecular weight HA molecules (300 kDa and 800 kDa) and the hydroalcoholic extract from aerial parts of *Salvia haenkei*. To obtain the extract of *Salvia haenkei*, plant material was harvested, put in a ventilated stove at 45 °C for 24 h, and then grounded into a fine powder. Dried powdered plant material was placed in a percolator and subjected to six cycles of extraction with water/ethanol (30–70% *v*/*v*) mixture. The obtained hydroalcoholic extract was filtered through a filter paper, concentrated under vacuum and dried at 40 °C in an oven under vacuum until complete evaporation of the solvent. Reference cream was identical to the test one, except for HA and the extract of *Salvia haenkei*. The composition of test cream is reported in Table 1.

Table 1. Composition of test cream IALUSET VITAL®.

CHEMICAL COMPOSITION
DISODIUM EDTA
XYLITYLGLUCOSIDE + ANHYDROXYLITOL + XYLITOL
POLYMETHYL METHACRYLATE
C14-22 ALCOHOLS AND C12-20 ALKYL GLUCOSIDE
ISONONYL ISONONANOATE
COCO CAPRYLATE/CAPRATE
HYDROXYETHYL ACRYLATE/SODIUM ACRYLOYLDIMETHYL TAURATE COPOLYMER + SQUALANE + POLYSORBATE 60
SODIUM HYALURONATE HMW (800.000 Da) (0.100%)
SODIUM HYALURONATE LMW (300.000 Da) (0.100%)
L-ARGININE
PHENOXYETHANOL, BENZOIC ACID, DEHYDROACETIC ACID, ETHYLHEXYLGLYCERIN
SALVIA HAENKEI EXTRACT (0.250%)
PURIFIED WATER

3. Results

3.1. Clinical Study: Patient Enrolment and Disposition

This study investigated how the cosmetic product IALUSET VITAL® affects the atopic dermatitis symptoms in adults, through a double-blind vehicle-controlled analysis. Caucasian male and female patients who showed a moderate form of AD, but no other comorbidities were selected (for enrolment criteria and characteristics of the patients, see Materials and Methods).

Patients were randomized into two demographically equivalent groups: the control group (n = 20, 15 females and 5 males) consisting of patients with a median age of 49 years (range 20–65), applied the vehicle cream; the active group (n = 20, 16 females and 4 males), including patients with a median age of 45 years (range 19–63), applied the IALUSET VITAL® cream. After randomization, control and active group patients also showed similar clinical characteristics at baseline: the median SCORAD index was 30.10 (IQR, Interquartile Range, 25.80–32.25) for the control group and 27.80 (IQR 25.37–31.07) for the active group (Table 2).

Table 2. Baseline demographics and AD characteristics.

	Control Group (Vehicle)	**Active Group (IALUSET VITAL®)**
Subjects enrolled (n)	20	20
Ethnicity		
Caucasian (n)	20	20
Gender		
Female n (%)	15 (75)	16 (80)
Male n (%)	5 (25)	4 (20)
Age (years)		
median (range)	49 (20−65)	45 (19−63)
SCORAD Median (IQR)	30.10 (25.80−32.25)	27.80 (25.37−31.07)
POEM Median (IQR)	10.50 (8.00−12.00)	9.00 (6.25−12.00)
Itching sensation Median (IQR)	5.25 (4.02−6.32)	4.95 (3.87−6.00)
Skin moisturization Median (IQR)	25.30 (20.75−31.13)	25.05 (20.70−30.48)
TEWL Median (IQR)	15.95 (12.10−20.03)	15.80 (12.68−20.28)

3.2. Efficacy Endpoints

Objective severity measures of AD symptoms were reduced in a statistically significant manner by IALUSET VITAL®, which induced a continuous decrease of SCORAD index over a 4-week treatment period. At the end of the treatment period, the median and mean changes in the SCORAD index from the baseline were respectively of −11.55 and −12.57 points in the active group compared with −6.35 and −7.42 points induced by the vehicle in the control group ($p_{active\ vs.\ control} = 0.003$). In addition, in the active group, the variance was reduced by −3.04 points while, in the control group, it was increased by 44.78 points. Overall, these data indicate that IALUSET VITAL® treatment is effective on most AD patients (Figure 2A, Tables 3 and 4).

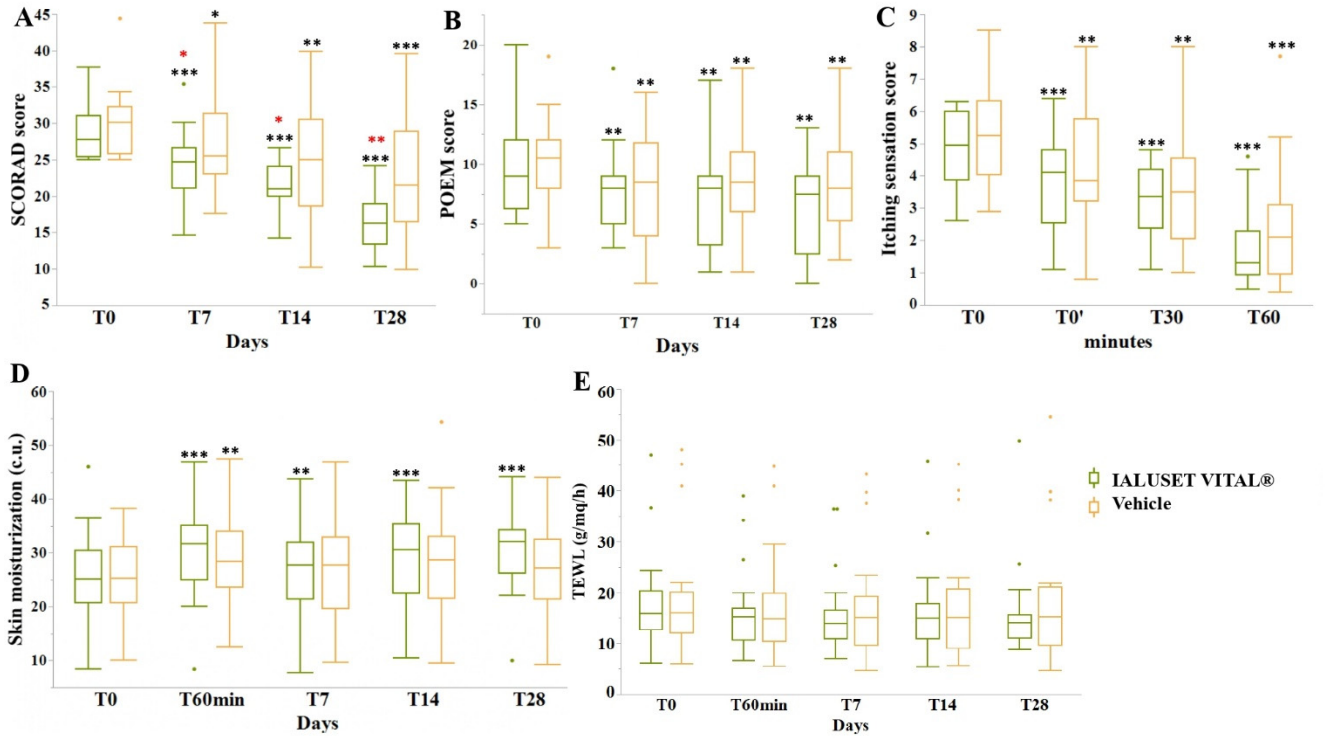

Figure 2. Efficacy outcomes in adults with moderate atopic dermatitis at the indicated time points. (**A**) SCORAD index was evaluated by the investigator; (**B**) POEM and (**C**) itching sensation scores were evaluated by patients; (**D**) Skin moisturization and (**E**) TransEpidermal Water Loss (TEWL) were established through non-invasive bioengineering techniques as indicated in Materials and Methods. Dots beyond the bounds of the whiskers denote outliers. Black asterisks indicate significant change from baseline for each group. Red asterisks indicate differences between active and vehicle group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Subjective measurement tools also revealed that IALUSET VITAL® treatment reduced eczema and pruritus severity from a moderate to a mild degree. In particular, at week 4, the median and mean change in POEM score from baseline were respectively of −2.50 and −3.20 points in the active group ($p < 0.01$) and of −1.00 and −1.90 points in the vehicle group ($p < 0.01$). No statistically significant differences were observed between the active and control group (Figure 2B, Tables 3 and 4).

Similar results were observed as concerns the evaluation of itching sensation (Figure 2C, Tables 3 and 4). Indeed, IALUSET VITAL® significantly reduced itching from a median baseline score of 4.95 (IQR 3.87–6.00) to 4.10 (IQR 2.55–4.80) as it is immediately after application ($p < 0.001$). This score has been continuously decreased to 1.30 (IQR 0.92–2.27) at 60 min. Total mean change from baseline was −3.15 ($p < 0.001$). The vehicle-induced effect on patients was also significant, although at T0′ and T30 the effect was more variable. Overall, the vehicle also significantly induced a total reduction in itching sensation from a median baseline score of 5.25 (IQR 4.02–6.32) to 2.10 (IQR 0.95–3.10). Total mean change

from baseline was −2.77 ($p < 0.001$). No statistically significant differences were observed between the two groups.

Table 3. Scores of all parameters determined at the indicated time points according to the study design in control and active groups (median, mean, and variance values are shown).

			Baseline (T0)	T0′	T30min	T60min	T7	T14	T28
Vehicle	Median (IQR)	Scorad	30.10 (25.80–32.25)	–	–	–	25.55 (23.00–31.38)	25.05 (18.68–30.50)	21.50 (16.48–28.86)
		Poem	10.50 (8.00–12.00)	–	–	–	8.50 (4.00–11.76)	8.50 (6.00–11.00)	8.00 (5.25–11.00)
		Itching	5.25 (4.03–6.33)	3.85 (3.23–5.76)	3.50 (2.05–4.55)	2.10 (0.95–3.10)	–	–	–
		Skin Moisturization	25.30 (20.75–31.13)	–	–	28.35 (23.60–34.05)	27.75 (19.70–32.90)	28.65 (21.55–33.08)	27.20 (21.35–32.50)
		TEWL	15.95 (12.10–20.03)	–	–	14.75 (10.38–19.80)	15.10 (9.65–19.15)	15.00 (9.05–20.65)	15.20 (9.73–21.08)
	Mean	Scorad	30.09	–	–	–	27.41 ($p < 0.05$)	24.92 ($p < 0.01$)	22.67 ($p < 0.001$)
		Poem	10.00	–	–	–	8.05 ($p < 0.01$)	8.35 ($p < 0.01$)	8.10 ($p < 0.01$)
		Itching	5.26	4.27 ($p < 0.01$)	3.69 ($p < 0.01$)	2.49 ($p < 0.001$)	–	–	–
		Skin Moisturization	25.93	–	–	29.20 ($p < 0.01$)	27.24	28.71	27.26
		TEWL	18.79	–	–	17.48	17.42	17.51	18.25
	Variance	Scorad	20.90	–	–	–	37.56	52.69	65.68
		Poem	13.79	–	–	–	19.63	15.61	15.46
		Itching	2.11	2.78	3.71	3.30	–	–	–
		Skin Moisturization	55.38	–	–	68.17	80.35	101.69	68.15
		TEWL	146.83	–	–	118.91	118.36	128.57	157.39
IALUSET VITAL®	Median (IQR)	Scorad	27.80 (25.38–31.08)	–	–	–	24.70 (21.13–26.63)	21.00 (19.95–24.13)	16.25 (13.45–18.98)
		Poem	9.00 (6.25–12.00)	–	–	–	8.00 (5.00–9.00)	8.00 (3.25–9.00)	7.50 (2.50–9.00)
		Itching	4.95 (3.88–6.00)	4.10 (2.55–4.80)	3.35 (2.38–4.20)	1.30 (0.93–2.28)	–	–	–
		Skin Moisturization	25.05 (20.70–30.48)	–	–	31.70 (24.95–35.08)	27.65 (21.48–32.00)	30.60 (22.58–35.38)	32.05 (26.23–34.23)
		TEWL	15.80 (12.68–20.28)	–	–	15.20 (10.73–16.95)	13.90 (10.90–16.63)	14.95 (10.98–17.83)	14.10 (11.08–15.58)
	Mean	Scorad	28.96	–	–	–	24.43 ($p < 0.001$)	21.51 ($p < 0.001$)	16.40 ($p < 0.001$)
		Poem	9.70	–	–	–	7.80 ($p < 0.01$)	7.35 ($p < 0.01$)	6.50 ($p < 0.01$)
		Itching	4.93	3.75 ($p < 0.001$)	3.15 ($p < 0.001$)	1.78 ($p < 0.001$)	–	–	–
		Skin Moisturization	25.63	–	–	30.50 ($p < 0.001$)	27.80 ($p < 0.01$)	29.26 ($p < 0.001$)	31.06 ($p < 0.001$)
		TEWL	17.84	–	–	16.34	15.88	16.36	15.94
	Variance	Scorad	16.96	–	–	–	19.91	11.18	13.91
		Poem	17.80	–	–	–	11.96	17.92	17.11
		Itching	1.51	2.38	1.26	1.45	–	–	–
		Skin Moisturization	69.64	–	–	75.50	70.74	69.11	59.67
		TEWL	91.89	–	–	69.61	65.91	82.09	78.77

Table 4. Changes from baseline for each parameter analyzed at the indicated times in the two study groups. The median of differences was calculated as the 50th percentile of all individual differences from baseline; the mean of differences was calculated as the average of all individual differences from baseline.

		Changes from Baseline											
		Vehicle						IALUSET VITAL ®					
		T0′	T30min	T60min	T7	T14	T28	T0′	T30min	T60min	T7	T14	T28
Median	Scorad	–	–	–	−0.50	−4.35	−6.35	–	–	–	−2.05	−6.80	−11.55
	Poem	–	–	–	−1.50	−1.50	−1.00	–	–	–	−1.00	−1.50	−2.50
	Itching	−0.85	−1.00	−2.65	–	–	–	−1.10	−1.40	−2.85	–	–	–
	Skin Moisturization	–	–	2.79	0.99	1.36	1.98	–	–	4.31	1.75	2.83	4.41
	TEWL	–	–	−0.05	−0.85	−1.20	−1.10	–	–	−0.65	−1.15	−0.75	−1.95
Mean	Scorad	–	–	–	−2.68	−5.17	−7.42	–	–	–	−4.54	−7.45	−12.57
	Poem	–	–	–	−1.95	−1.65	−1.90	–	–	–	−1.90	−2.35	−3.20
	Itching	−1.00	−1.58	−2.77	–	–	–	−1.18	−1.78	−3.15	–	–	–
	Skin Moisturization	–	–	3.27	1.31	2.78	1.33	–	–	4.87	2.17	3.62	5.43
	TEWL	–	–	−1.31	−1.37	−1.28	−0.54	–	–	−1.50	−1.96	−1.48	−1.90

Furthermore, an improvement in moisturization of stratum corneum was observed in the active group as early as 60 min after the initiation of treatment. The median and mean changes in the moisturization index from the baseline were respectively of 4.31 and of 4.87 points ($p < 0.001$). These results induced by IALUSET VITAL® remained nearly

constant during the four weeks of treatment. A statistically significant increase of the skin moisturization index has also been recorded in the vehicle treated group only at 60 min after the first product application. No statistically significant difference was observed between the two groups (Figure 2D, Tables 3 and 4).

Finally, to evaluate if *perspiratio insensibilis* was affected from IALUSET VITAL® treatment, the trans-epidermal water loss (TEWL) was monitored. Data revealed that both IALUSET VITAL® and vehicles did not alter the water perspiration out of the skin throughout the treatment period (Figure 2E, Tables 3 and 4).

3.3. Tolerance and Safety

Tolerance and safety were assessed for all the patients during the entire study period. The enrolled subjects did not show neither the occurrence of new physical (erythema, oedema, desquamation, other) and functional signs (burning, itching, other) nor the worsening of basal physical and functional signs. Therefore, both IALUSET VITAL® and vehicle cream were well tolerated by all the subjects during the study duration.

The safety of IALUSET VITAL® was also assessed in a previous clinical study on the efficacy of the cream in reducing the effects of skin ageing [20], where the cream was revealed to be highly tolerated with no adverse reactions reported by any of the 50 subjects enrolled.

4. Discussion

Atopic dermatitis is mainly characterized by dysfunctions of the skin barrier and an uncontrolled inflammatory response. HA has been shown to play an important role in regulating homeostasis of the skin, especially in maintaining selective permeability of the epidermis and controlling inflammatory response. Moreover, because of its hygroscopic property, HA provides a hydrated microenvironment which facilitates the transport of nutrients through the tissue [25]. Finally, HA directly affects the function of skin cells by mediating signaling events that control the proliferation/differentiation of keratinocytes and lamellar bodies production, important mechanisms for maintaining selective permeability and repair of the skin [11,13]. It was also demonstrated that topical application of HA induces keratinocyte proliferation/differentiation and increases epidermal thickness and skin barrier repair [14].

Immune response in subjects with AD is dysfunctional, characterized by the release of many pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukins [26]. Several authors have shown that HA reduces inflammatory response by downregulating the expression of pro-inflammatory and upregulating anti-inflammatory molecules [27–31]. Indeed, Kim et al. observed that HA decreases skin lesions in an atopic dermatitis model of DNFB-treated Nc/Nga mice [28].

In patients with AD, claudins' expression levels are reduced [32,33]. These proteins together with the occludin form a family of proteins that are the most important components of the tight junctions (TJs). In turn, TJs are critical in the functioning of the skin barrier because defective TJs increase paracellular permeability, resulting in an enhanced flux of environmental factors such as irritants, microbial products, toxins, and allergens, which, crossing the skin surface, trigger the immune response [34]. Recently, the extract of *Salvia haenkei* was shown to increase occludin expression as well as to control the expression and localization of filaggrin, a key marker of keratinocytes' differentiation. Thus, the extract of *Salvia haenkei* reinforces the adhesion between the cells and favors the maintenance of the barrier integrity [22].

Considering the mentioned observations, we performed this clinical study in order to assess on AD patients the efficacy of IALUSET VITAL® cream, a cosmetic containing two molecular weights of hyaluronic acid (300 kDa and 800 kDa) and the extract of *Salvia haenkei*.

This study clearly showed that the regular use of IALUSET VITAL® progressively and significantly reduces AD severity and improves SCORAD, POEM, itch, and stratum

corneum moisturization scores. After one week of treatment, a significant decrease of the SCORAD index was already observed in the active group compared to the control group. Interestingly, IALUSET VITAL® treatment improved AD severity from moderate to a mild degree, in a time-dependent manner as shown by the progressive reduction of the mean change of SCORAD index from baseline by 42% compared with 25% induced by vehicles in the control group at week 4.

At the end of treatment, 70% and 65% of the patients in the active and control group, respectively, reported a reduction of the POEM score less than the median value at T0. In particular, only the active group showed 10% of patients with total remission of symptoms.

As concerns the evaluation of itching sensation, immediately after treatment, 80% and 65% of the patients in the active and control group, respectively, showed a reduction of itch score less than the median value at T0. Moreover, 60 min after the treatment, a reduction of itch score lower than the median value at T0, was recorded in 100% and 95% of the patients in the active and control group, respectively.

However, both for POEM and itch score, the differences between the two treatment groups did not appear to be statistically significant.

The treatment with IALUSET VITAL® led to a significant increase of skin hydration throughout the treatment period while the vehicle induced a more variable effect in the control group. Paradoxically, although the TEWL analysis showed a positive trend of IALUSET VITAL®, in terms of effectiveness compared to vehicles, no statistically significant difference has been shown. Similar findings have been reported in other studies on moisturizers [35–37]. Our results may not be consistent for several reasons. Firstly, the relationship between skin dryness and TEWL is complex, whereby changes in dryness may not necessarily reflect simultaneous changes in TEWL [38]. Then, standardization of TEWL measurements can be technically difficult, while corneometer is an effective and sensitive tool to determine skin moisturization [39]. Therefore, the latter method is more sensitive to measure the skin barrier function than TEWL in AD patients and a larger sample size may be necessary to clarify this discrepancy and achieve a statistically significant trend in TEWL changes.

The vehicle used in this study was an emollient base cream, with the same composition of IALUSET VITAL® except for the key ingredients hyaluronic acid and extract of *Salvia haenkei*. Due to the presence in the formulation of some humectant and emollient agents such as xylitylglucoside, anhydroxylitol, xylitol, isononyl isononanoate, coco caprylate/caprate, and l-arginine, the vehicle cream exhibits some beneficial moisturizing effects that should be taken into consideration when statistically significant differences in effectiveness between the active and control group have not been noted. Indeed, it is well known that emollients make the epidermis softer and more pliable, and they are effective in increasing skin hydration, improving barrier function, and reducing itching in AD [40].

Thus, the efficacy of IALUSET VITAL® is guaranteed by the good emollient properties resulting from a well-designed basic formulation and, above all, the addition of active ingredients hyaluronic acid and extract of *Salvia haenkei* that greatly increase its effectiveness. In addition, IALUSET VITAL® cream was well-tolerated by patients. Overall, this study clearly shows that IALUSET VITAL® has a good safety profile and promotes the relief of the most common signs and symptoms of moderate AD, rapidly suppressing itch and reducing eczema severity.

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