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# Effects of a pH-Regulating Emollient Cream in Mild Atopic Dermatitis Patients with Moderate Localized Lesions

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## Keywords

Atopic dermatitis · Emollient cream · Skin pH · Skin hydration · Local SCORAD

## Abstract

**Introduction:** Increased skin pH values in patients with atopic dermatitis (AD) contribute to poor antimicrobial and permeability barrier functions of the skin. In practice, the majority of topical preparations available for dry skin conditions do not provide sufficient pH and buffering capacity for maintaining optimum skin surface conditions. To address this issue, we tested a novel zinc lactobionate preparation to determine whether the regular application would lower skin surface pH, and in doing so improve the condition of lesional skin. **Methods:** The assessment for local severity of AD was done with the Scoring Atopic Dermatitis Index (SCORAD) and skin dryness was assessed by capacitance measurement. **Results:** The results showed that the test product lowered skin pH and improved AD skin lesions from moderate to mild during 2 weeks of application. In the treated area a lowered pH of about 0.85 units was found. Together with the lowering of pH, the local SCORAD significantly improved from 8.3 on average down to 4.0, while in the untreated area, only a slight improvement (from 8.2 to 6.4) was found. **Conclusion:** Synergistic effects of the test

product's pH lowering and emollient properties might explain the observed improvements in clinical signs of AD and further research against a comparator would allow the specific contribution of pH modulation to these improvements to be unambiguously isolated.

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## Introduction

The pH of the skin, usually between 4.5 and 5.5, is intricately embedded in the pathophysiology of atopic eczema/dermatitis (AD) [1, 2]. Well-established triggers such as washing with harsh surfactants, for example, are known to elevate the pH of the skin surface [3, 4]. While skin surface pH can dramatically increase at lesional sites (pH 7.3/7.4), driven by inflammation, unaffected skin in AD patients is characterized by subtle changes of between 0.1 and 0.9 pH units [1, 5]. As a pivotal regulator of stratum corneum homeostasis, small increases in pH can result in dysbiosis of the skin microbiome, accelerated desquamation (skin shedding) resulting from protease hyperactivity, abnormal processing of lipids into the protective lipid lamellae that confers water permeability barrier function; digestion of endogenously produced

antimicrobial peptides and activation of pro-inflammatory cytokines [1, 6–8]. These pH-centric changes characterize the skin of AD patients and contribute to poor antimicrobial and permeability barrier functions of the skin, leaving it prone to dryness, irritation and colonization by *Staphylococcus aureus*.

Studies in animals have shown that lowering skin surface pH can prevent the development of hapten-induced dermatitis [9]. In humans, acidifying the skin is associated with an improvement in skin health, specifically enhanced skin permeability barrier function [10]. The ability of dermatological treatments to modulate the skin's pH has been elucidated by several studies. Schreml et al. [11] explored the effects of a 10% alpha hydroxyl acid (AHA) oil/water emulsion on the skin's pH and highlighted the potential of AHAs not only in superficial pH adjustment but also in influencing the pH gradient within the stratum corneum. Complementing this, Fürtjes et al. [12] demonstrated the effectiveness of a pH 5 oil-in-water emulsion in stabilizing skin surface pH after alkalization, such as that caused by soap use. Similarly, Behm et al. [13] reported significant reductions in skin pH in both healthy elderly and diabetic patients using a glycolic acid-containing water-in-oil emulsion adjusted to pH 4. Moreover, Fluhr et al. [14] expanded on these findings by investigating the impact of acidic skin care on compromised skin, following mild tape stripping. However, the acids used to bring down the skin pH, including AHAs like lactic acid, are known skin sensitizers that can induce stinging when used inappropriately [15]. In practice, the majority of topical preparations currently available for dry skin conditions like AD exhibit a pH and buffering capacity inappropriate for maintaining optimum skin surface conditions [16].

Skin pH measurement is a critical component in dermatological research, particularly for conditions like AD, where skin barrier function is a key factor. Various methods have been developed to measure skin pH, each with its unique advantages and limitations [17, 18].

The most frequently used method to assess the skin pH is a measurement with a planar glass electrode. This method is quick as a single measurement takes only a few seconds. It has been well established since 1955 [19].

The Scoring Atopic Dermatitis Index (SCORAD) [20] is the clinical instrument to assess AD severity with the most validation studies available [21]. In studies with an intra-individual comparison of differently treated lesions, a local SCORAD is frequently used [22]. The total area of the lesions is taken out of the assessment to obtain a local result.

Dry skin is a main characteristic of AD and often still remains after skin lesions have healed. A wide range of methods are available to measure skin moisture [23]. Capacitance measurement is a well-established method [24]. In clinical settings, this method is of advantage in a multi-parametrical design as quick non-invasive measurements are obtained that do not alter the measurement area.

Currently, there is a lack of studies investigating the effects of skin pH lowering preparation on AD patients. Thus, the aim of this study was to determine whether the regular application of a novel zinc lactobionate preparation lowers skin surface pH, and in doing so improves the condition of lesional skin in AD patients. In addition to maintaining a low skin pH, the preparation has been designed to restrict excessive stratum corneum protease activity and deliver key lipids deficient in the skin AD patients [25] to aid restoration of normal skin homeostasis. Local severity of AD was assessed with the SCORAD, and skin dryness was assessed by capacitance measurement.

## Materials and Methods

### Study Design

This was an exploratory, randomized, observer-blind, controlled (treated vs. untreated) study, carried out at proderm GmbH, Germany (since 2022, SGS proderm GmbH, Germany). The study visits were performed at baseline (Day 1) and Day 15. Test product was applied on the randomized treated arm twice daily for 2 weeks.

### Participants

Eligible patients with mild AD with moderate local lesions were comprised of female or male volunteers from 4 to 65 years old (without any fixed ratio of age groups), with at least two comparable lesions (at least a local SCORAD of 6 as mean over the two lesions, out of maximum 18), diagnosed by a dermatologist, ideally in contralateral position were included in the study. Further, patients signed written informed consent, or, for underage patients (<16 years), this was signed by their parents/legal guardians to let the child participate in the study. Patients expressed willingness to actively participate in the study and to come to the scheduled visits, and where appropriate, the willingness of the parents/legal guardians to actively support the participation of their child in the study and to accompany them to the scheduled visits was assured.

Female patients in case of pregnancy or lactation were excluded from the study. Further exclusion criteria were (1) patients that are drug addicts, alcoholics, AIDS, HIV-positive, or infectious hepatitis if known; (2) conditions which exclude participation or might influence the test reaction/evaluation; (3) participation or being in the waiting period after participation in similar cosmetic and/or pharmaceutical studies; (4) active skin disease at the test area; (5) one of the following illnesses that might require regular systemic medication: insulin-dependent diabetes, cancer, rheumatic disease (except AD); (6) documented allergies to cosmetic products and/or ingredients; (7) moles, tattoos, scars, irritated skin, hairs, etc., at the test area that could influence the investigation; (8) regular use of tanning beds within the last 2 years; (9) systemic therapy with immuno-suppressive drugs (e.g., corticosteroids) and/or antihistamines (e.g., antiallergics) within the last 30 days prior to the start of the study; (10) topical corticosteroids at the test area within the last 2 weeks prior to the start of the study; (11) supporting therapy against AD (UV therapy, probiotic homeopathy, etc.) within the last 2 weeks prior to the start of the study and antiseptic or antibacterial wash or topical products within 4 weeks prior to start of the study. Remuneration was paid to the patients.

### Interventions

#### Test Product

The test product is a novel emollient cream with patented technology to sustainably lower skin pH [26]. It contains lactobionic acid, zinc oxide, butylene glycol, PEG-240/HDI copolymer bis-decyltetradeceth-20 ether, trideceth-6, glycerin, ethylhexylglycerin, hydrogenated polydecene, methyl glucose sesquistearate, PEG-20 methyl glucose sesquistearate, myristyl alcohol, behenyl alcohol, hydroxypropyl bispalmitamide MEA, cholesterol, linoleic acid, acrylates/C10-30 alkyl acrylate crosspolymer, sodium hydroxide, and water. It was applied, according to normal use conditions which are approximately 2 mg/cm<sup>2</sup>, twice daily in the morning and in the evening at home for 2 weeks at the body area. Precisely, at one of two contralateral skin areas with comparable lesions of AD (specified by the dermatologist, local SCORAD of at least 6 [two lesions averaged]). The other area was untreated. Size of the test sites was approximately 5 × 5 cm located on volar forearms (1), dorsal forearms (7) inner elbow (14), back (2), lower leg (2), and back of the knee (4).

#### Procedures and Assessments

During visits, patients remained at least 30 min in a climate-controlled room. The following measurements were performed at baseline and Day 15: skin surface

pH using Skin pH Meter pH 900 pc (Courage & Khazaka, Cologne, Germany), skin hydration using a Corneometer cm 825 (Courage & Khazaka, Cologne, Germany), and visual evaluation with local SCORAD (SCORing Atopic Dermatitis).

At baseline and Day 15, two skin pH measurements per test area were performed. The contact surface of a specific wetted glass electrode was placed gently onto the measurement area of the skin to obtain the skin pH value. Skin hydration was evaluated with five corneometer measurements per test area. The measuring principle was based on changes in the capacitance (a.u.) of the measuring head, functioning as a capacitor. An electrical field is built between the gold conductors. By these means, the dielectricity of the upper skin layer was measured. Because the dielectricity varies as a function of the skin's water content, the stratum corneum hydration can be measured. The visual evaluation was performed by a dermatologist or trained physician. The objective skin status on the atopic lesions (erythema, edema and papules, weeping and crusts, excoriation, lichenification, dryness [dryness was evaluated on the non-lesional areas]) were evaluated on a 4-point scale from 0 (absent) to 3 (severe). The local SCORAD per test area is the sum of all scores for all six abovementioned parameters (minimum = 0, maximum = 18). Atopic lesion with a local SCORAD of >6 is considered moderate severity whereas a local SCORAD of <6 is deemed as mild in severity.

#### Sample Size

As this was an exploratory study no sample size calculation was performed. The sample size was chosen based on the experience of the test institute with this type of study.

#### Randomization

Treatments were randomly assigned to the left and right sides of the body, in a balanced manner according to the local SCORAD using a randomization tool of the eCRF system (SecuTrial®). The program determines for each subject if the right or left lesion has a higher score or if both are equally scored and then assigns the treatments to the sides in a balanced way.

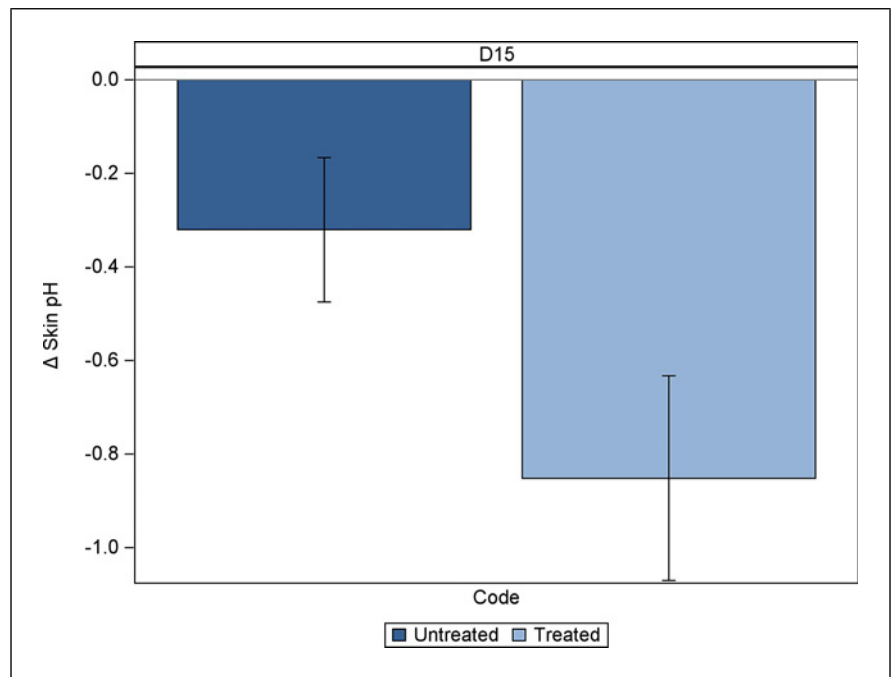
#### Blinding

In this observer-blinded study, the dermatologist who did the scoring and the study technician who applied the product were placed in different rooms.

**Table 1.** Skin surface pH – mean values, standard deviations, and comparison of treatments on differences to baseline by paired *t* test

Treatment comparison vs. untreated					<i>p</i> values
time	area	<i>n</i>	mean values±SD	differences to BL±SD	
BL	Untreated	29	5.07±0.34	–	–
	Treated	29	5.09±0.29	–	–
D15	Untreated	29	4.75±0.33	–0.32±0.41	–
	Treated	29	4.24±0.47	–0.85±0.57	<b>&lt;0.001</b>

Bold *p* value: significant ( $p \leq 0.05$ ). BL, baseline.



**Fig. 1.** Change in skin surface pH. Bar chart with mean values and 95% confidence intervals of differences to baseline ( $n = 29$ ).

### Statistical Methods

For skin pH, skin hydration, and local SCORAD, *N*, mean, standard deviation, median, minimum, maximum and 95% confidence limits were analyzed for raw data and differences to baseline by treatment and assessment time. For local SCORAD (single items), *N*, mean, standard deviation, median, minimum and maximum were analyzed. Count of single scores and count of scores greater than 0 were presented for raw data per treatment, assessment time, and item.

A significance level of 0.05 (alpha) was chosen for statistical analysis. Due to the explorative character of the study, no adjustment for multiplicity was done. For the skin pH and skin hydration, local SCORAD

comparison of treatments (untreated vs. treated) was performed on differences to baseline by paired *t* test for each assessment time and parameter. The computation of the statistical data was carried out with commercially available statistics software (SAS for Windows).

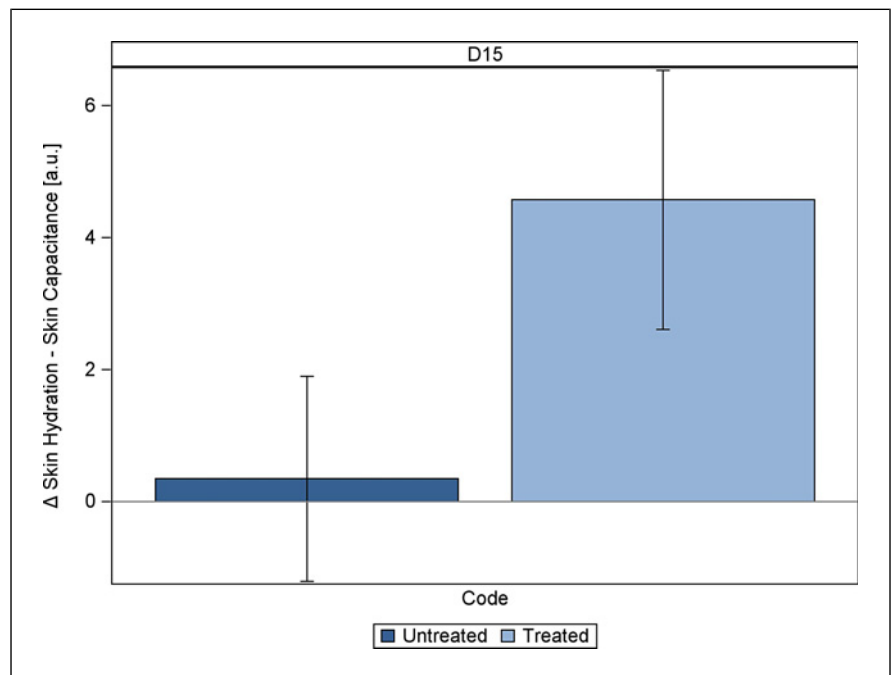
### Results

A total of 30 patients were included and 29 finished the study without major deviations. The panel was composed of 10 male and 19 female patients with a broad age range from 6 to 64 years, mean age of  $30.0 \pm 19.4$  years, with fair skin type. There was one drop-out

**Table 2.** Skin hydration – mean values, standard deviations, and comparison of treatments on differences to baseline by paired *t* test

Treatment comparison vs. untreated					<i>p</i> values
time	area	<i>n</i>	mean values (a.u.)±SD	differences to BL±SD	
BL	Untreated	28	11.39±7.44	–	–
	Treated	28	11.68±6.81	–	–
D15	Untreated	28	11.74±6.12	0.35±4.01	–
	Treated	28	16.25±7.48	4.57±5.06	<b>&lt;0.001</b>

Bold *p* value: significant ( $p \leq 0.05$ ). BL, baseline.



**Fig. 2.** Change in skin hydration. Bar chart with mean values and 95% confidence intervals of differences to baseline ( $n = 28$ ).

without relation to the test product. In terms of safety, no adverse reactions occurred during the study. The study test dates were from December 7, 2020, to February 15, 2021.

#### Skin Surface pH

For skin surface pH, improvement after 2 weeks of test product application was observed. Namely, the differences from the end of treatment to baseline (Day 15 compared to Day 1) showed decreased mean values for both the untreated and treated areas (Table 1). The comparison of treatments on differences to baseline showed a significantly lower mean value ( $p < 0.001$ ) and therefore more acidic skin pH for treated than for the untreated areas (Fig. 1).

#### Skin Hydration

An increase in corneometer values (measured by skin capacitance), related to an increase in skin hydration, was clearly observed at the areas treated with test product over the 2-week treatment. However, there is only a very slight increase in skin hydration at the untreated test area (Table 2). The comparison of treatments based on differences to baseline showed a significantly higher mean skin hydration ( $p < 0.001$ ) for the test area treated with the test product compared to the untreated area (Fig. 2).

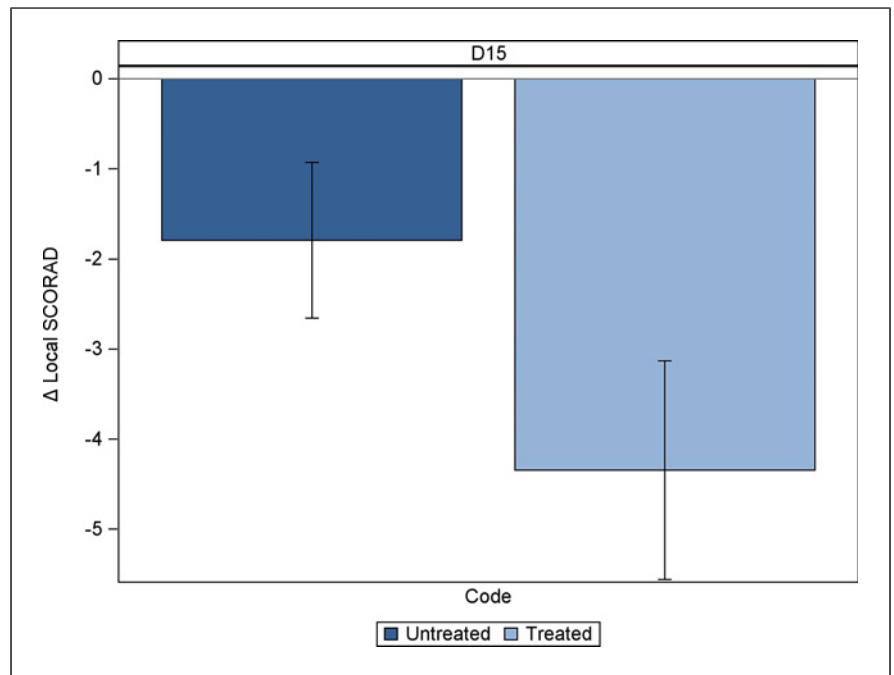
#### Local SCORAD

The mean values and standard deviations of sum scores for local SCORAD at both test areas by a dermatologist, as well as the results of treatment comparison

**Table 3.** Local SCORAD – mean values, standard deviations, and comparison of treatments on differences to baseline by paired *t*-test

Treatment comparison vs. untreated					<i>p</i> values
time	area	<i>n</i>	mean values (a.u.)±SD	differences to BL±SD	
BL	Untreated	29	8.2±2.4	–	–
	Treated	29	8.3±2.4	–	–
D15	Untreated	Untreated	29	6.4±2.6	–
	Treated	Treated	29	4.0±2.8	<b>&lt;0.001</b>

Bold *p* value: significant (*p* ≤ 0.05). BL, baseline



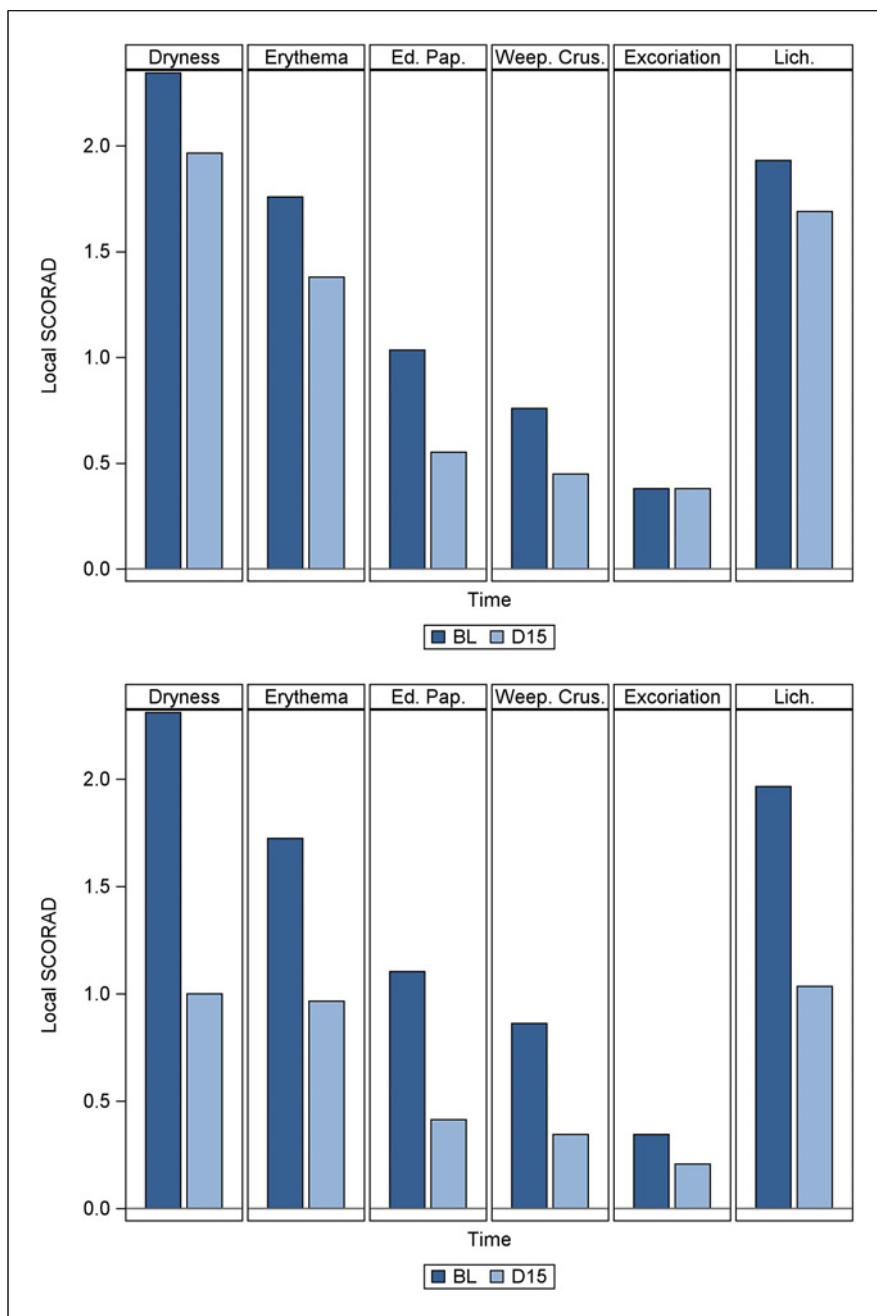
**Fig. 3.** Local SCORAD. Bar chart with mean values and 95% confidence intervals of differences to baseline (*n* = 29).

based on differences to baseline by paired *t* test, are shown in Table 3. The local SCORAD represents the sum of the scores of the 6 abovementioned parameters as assessed on the selected lesional test areas. The severity was rated from 0 = absent to 3 = severe. The lowest possible sum value was “0” and the highest possible value “18.” The lower the local SCORAD value, the better the skin condition was. The mean values of the local SCORAD decreased for both test areas on Day 15 in comparison to Day 1 (baseline), showing a higher decrease for the treated test area. Further, the comparison of treatments based on differences to baseline showed a statistically significant reduction in mean local SCORAD values (*p* < 0.001) for the treated test area compared to the untreated

test area, reflecting the positive effect of the use of the test product (Fig. 3). A breakdown of the various parameters in local SCORAD for both the treated and untreated side between the baseline and Day 15 is shown in Figure 4.

### Discussion

In the presented study, children and adult patients with mild AD having moderate severity lesions at the target treatment areas (local SCORAD >6) were included. Treatment with a novel emollient cream with patented skin pH-lowering technology for 2 weeks led to an improvement in the condition of these lesions.



**Fig. 4.** Local SCORAD. Bar chart with mean values for comparison of untreated area (upper figure) and treated area (lower figure) at baseline (BL) and Day 15 (D15) ( $n = 29$ ). Ed. Pap, edema and papules, Weep. Crus, weeping and crusts; Lich., lichenification.

A significant lowering of the skin pH by about 0.85 units was observed after 2 weeks of treatment with the test product. On the other hand, only a slight pH lowering of approximately 0.3 units was found on the untreated control lesions. It is probable that natural causes, like a change in outdoor temperature and humidity, led to this slight change in the untreated areas. Even a small increase in skin pH has various effects on the skin, importantly including an elevation in protease

activity, specifically chymotrypsin-like activity, which leads to heightened rates of desquamation. It has been shown that an elevation of skin surface pH by about 0.5 units results in a 2-fold increase in chymotrypsin-like activity [27]. FLG loss-of-function mutations, that increase the risk of developing AD, are associated with changes in skin surface pH of just 0.24 units on average (0.32 units in the context of AD) [28]. Together this suggests that the treatment has brought about a

physiologically relevant reduction in skin surface pH. Importantly skin surface pH levels were maintained within the physiologic range of 4–6 [19].

Together with the lowering of skin pH, the local SORAD significantly improved from 8.3 on average down to 4.0 (51.81% reduction) at the treated test area, while only a slight improvement from 8.2 to 6.4 (21.95% reduction) was observed on the untreated test area. A 2-week treatment with the test product significantly improved the severity of atopic lesions from mainly moderate to mild. The dryness sub-scores of the local SCORAD index decreased by 56.71% at the treated test area by the end of treatment. The clinical improvement in dryness evaluated visually is further confirmed in the change in capacitance measuring skin hydration.

As a typical sign of AD, the patients had very dry skin on the test areas. Corneometer readings clearly below 30 were measured, indicating very dry skin [29]. At baseline, an average Corneometer value of slightly above 10 was measured, even indicating extremely dry skin. This state did not improve in the untreated area, while an increase to an average of 16 units was observed in the test product treated area. Still, the skin was very dry, but the increase in skin moisture was clear and of high statistical significance.

In this study, significant improvements in AD lesions and skin dryness were observed after 2 weeks of regular topical treatment with the test product compared to a no-treatment control. These outcomes demonstrate the ability of the test product to alleviate some of the symptoms of mild AD. However, inclusion of other ingredients in the test product formulation, with possible effects on skin barrier function, means we cannot conclusively isolate the contribution of zinc lactobionate. That being said, zinc lactobionate is the primary ingredient in the formulation that directly contributes to pH lowering efficacy of the test product. Moreover, a cream containing zinc lactobionate was recently investigated by Andrew et al. [30] to further evaluate its impact on AD patients, and demonstrated that compared to a vehicle control, the zinc lactobionate-containing formulation reduced skin surface pH, TEWL and chymotrypsin-like protease activity, and increased the skin hydration; which are crucial for skin health in AD patients. The clinical improvements in SCORAD and skin hydration as well as the test product's effect on the pH of the skin observed in our study support these results.

The test product contains zinc ions which are a natural inhibitor of kallikrein-related peptidases (KLKs) that

drive desquamation and inflammation via PAR2 receptor activation [31]. Thus, it could be the case that the combination of zinc ions and lactobionic acid acts not only as a pH buffering agent but as a direct modulator of protease activity too.

We consider it very likely that the synergistic effects of the test product's skin pH lowering efficacy, the use of zinc oxide and the formulation's emollient effect all contributed to the improvements in AD lesions and skin dryness found in our study.

#### *Study Limitation and Further Perspectives*

In this study, we had no comparator with neutral pH. To investigate the treatment effect of the complete product in a controlled manner, an untreated area was chosen for comparison. However, testing against comparator (treated area) would isolate and control for the effect of pH modulation versus emollient effects and thus would be the topic of a further study to conclusively determine the role of this novel pH modulating technology considering the positive effects on skin hydration and AD lesions observed in this study.

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#### **Statement of Ethics**

The study protocol was reviewed and approved by an Independent Institutional Review Board (IRB) of SGS proderm in November 2020 (IRB Approval No. 2020/023). This study on human patients was executed according to the principle requirements of the Declaration of Helsinki and according to the main principles of Good Clinical Practice (GCP). Participants were informed orally and in writing about the study details including potential risks and inconveniences. They provided their written consent before they were included in the study. Where the participant was under the age of 18 years, written informed consent was obtained from the participants' parent/legal guardian/next of kin to participate in the study before they were included in the study.

#### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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## Author Contributions

Sue Phay Ng, Stephan Bielfeldt, Sabrina Laing, Simon Danby, and Michael Cork have all contributed to the conception of this study as well as the drafting of this manuscript and have critically reviewed and approved this final version for publication.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding authors.

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