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Fragility of epidermis: acne and post-procedure lesional skin

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Abstract
‘Fragile skin’, or skin with lower resistance to aggressors, can be broadly classified into four causal categories: constitutional (age-dependent or associated with specific vulnerable locations on the body, e.g. eyelids), pathological (related to disease), circumstantial (related to environmental or internal factors, e.g. stress) and iatrogenic (caused by medical interventions or treatments). In this supplement, we focus on the fourth category, the iatrogenic origin of fragile skin and the role that dermo-cosmetics can have in restoring the natural protective function of the skin following treatments for skin diseases and medical interventions. We present epidemiological data on the prevalence of fragile skin in three different geographical regions, and the results of two randomized controlled studies investigating the efficacy and tolerability of dermo-cosmetics in combination with topical acne treatment and following physical skin damage. Overall, we found that prevalence across the three regions (23% in Germany, 41% in UAE, 56% in Taiwan) reflected previous global estimates (24–53%) across skin types, with significant associations found with environmental and lifestyle factors, such as stress, humidity and pollution. The iatrogenic effects of topical acne treatments can result in poor compliance or use of over-the-counter moisturizers, which may reduce treatment efficacy. Dermo-cosmetics were found to aid in restoration of fragile skin caused by the acne topical retinoid treatment adapalene 0.1% gel, by reducing transepidermal water loss and improving skin hydration, as well as reducing the side-effects such as skin irritation that are frequently associated with topical retinoids. Additionally, dermo-cosmetic products were found to accelerate wound closure following skin damage in a laser ablation model and reduced the duration of post-procedural side-effects such as itching and burning.

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Conflicts of interest
MSA is Medical Director of A-DERMA Dermatological Laboratoires and employee of Pierre Fabre Dermo-Cosmétique. ABR, MDT, CP, VM and AB are employees of Pierre Fabre Dermo-Cosmétique.

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Overview
The skin acts as a barrier between the external and internal environments, aiding in homeostatic regulation, prevention of excessive water loss and protection against external agents such as bacterial, chemical and physical stressors. Any disruption to this epidermal barrier can reduce resistance to immunological and physical aggressors, and can leave the skin open to development of pathological conditions. This ‘fragile skin’, defined as skin with a lower resistance to aggressors, is broadly classified into four categories, based on the origin of the fragility: constitutional (age-dependent or associated with specific vulnerable locations on the body e.g. eyelids), pathological (related to disease), circumstantial (related to environmental or internal factors, e.g. stress) and iatrogenic (caused by medical interventions or treatments). The term ‘fragile skin’ encompasses a wide spectrum of causal conditions, ranging from perceived skin reactivity to life-threatening diseases. Often fragile skin has multifaceted origins, with a number of these factors contributing to vulnerability of the epidermis, for example treatment for a skin condition in combination with the condition itself.

To better understand the global variance in prevalence and factors influencing the perception of fragile skin, we conducted...
three cross-sectional studies in populations in Germany, the United Arab Emirates (UAE) and Taiwan. Questionnaire data were used to identify contributing factors (e.g. gender, environmental and social conditions, skin type and skin conditions) and the prevalence of perceived fragile skin. Overall prevalence was lowest in Germany (23%), intermediate in UAE (41%) and highest in Taiwan (56%). These values reflect previous global prevalence estimates of 24–53% across skin types, as well as specific estimates for Caucasian and Asian skin types. The recent epidemiological results found significant associations between the perception of having fragile skin and reporting of skin symptoms and diseases across all three studied populations. Significant associations were also found between reporting of fragile skin and environmental and lifestyle factors such as stress (all three countries), and pollution, humidity and weather conditions (Taiwan and Germany). Despite being a subjective condition with no defining pathology, the overall prevalence of perceived fragile skin in a substantial proportion of the population and associations with skin symptoms indicate that this is a condition that individuals seek relief from and highlights the role that treatments for fragile skin can have in both restoring the skin barrier and on patients’ quality of life.

In this supplement, we focus on the fourth category, the iatrogenic origin of fragile skin, and the role that dermo-cosmetics can have in restoring the natural protective function of the skin following treatments for skin diseases and medical interventions. Many acne treatments, such as topical retinoids, can alter the skin barrier, causing an increase in transepidermal water loss, decreased skin hydration and skin irritation. These unwanted effects can lead to low compliance with treatment, or use of an over-the-counter moisturizer, which can lower the efficacy of the acne treatment. Similarly, medical interventions such as skin resurfacing treatments or surgery also disrupt the barrier function of the skin by removal of the stratum corneum and other skin layers, leaving the skin fragile and susceptible to irritation.

We present the results from two original randomized controlled studies in this supplement on iatrogenic fragile skin. In the first study, we investigated the effects of application of a dermo-cosmetic care product containing glycolic, lactic and salicylic acids and Rhealba® Oat Plantlets extract in combination with adapalene 0.1% gel in subjects aged 15–35 years with moderate acne vulgaris. Each side of the patient’s face was randomized to receive a daily application of dermo-cosmetic care product and adapalene (tested side) or adapalene only (control side), and assessments of tolerance and efficacy were performed over a 4-week study period. Overall, patient global assessment results were higher for the side of the face where the dermo-cosmetic was applied at 8, 15 and 29 days of treatment, and significant benefits in skin hydration and transepidermal water loss were observed by the 29th day of treatment, with no change to skin pH or impact on treatment efficacy.

In the second study included in this supplement, we investigated the efficacy and tolerability of another dermo-cosmetic containing Rhealba® Oat Plantlets extract for reducing irritation following physical skin barrier damage. In the study, four epidermal ablations were made using a laser on the inside surface of the forearm of each subject. Each ablation was randomized to receive the test product, a previous formulation of the test product, a comparator or no product. Wound closure was faster and skin barrier function restored more quickly with the test product than the comparator or no treatment. Any itching, burning or peri-lesional erythema was also resolved faster. The data from the study indicate a role for the dermo-cosmetic product in wound healing following skin procedures such as peelings, laser treatments and surgery, or following physical skin damage.

**Detail of two new clinical studies**

**Clinical study in acne**

**Evaluation of the efficacy and tolerability of a dermo-cosmetic care product based on Rhealba® Oat Plantlets Extract in combination with adapalene 0.1% gel in subjects with moderate acne vulgaris – a randomized comparative split-face study**

One of the major functions of the skin is as a protective barrier for the body against external factors such as mechanical impacts, pressure, temperature variations, micro-organisms, radiation and chemicals. Additionally, the skin functions as a regulator of fluid loss by providing a semi-impermeable barrier to the external environment. Disruption of the skin barrier can lead to a range of biological changes which compromise the barrier role, causing excessive transepidermal water loss (TEWL), reduced hydration of the stratum corneum and potential development of dermatological pathologies. Changes in the epidermal barrier result in ‘fragile skin’, a condition of the skin where the barrier function has been disturbed, leading to lower resistance to mechanical and immunological aggressors. Fragile skin can be categorized into four different types: constitutional (related to age or skin location), pathological (caused by a disease), circumstantial (caused by environmental factors, or internal factors such as stress) and iatrogenic (caused by medical interventions), and includes a wide range of causal conditions from perceived skin sensitivity to life-threatening skin diseases.

**Acne vulgaris** is a very common inflammatory skin disease of the sebaceous follicles, estimated to affect 9.4% of the population worldwide, with a prevalence of approximately 85% in adolescents. The main pathogenic factors of acne are increased sebum production, stimulated by circulating androgens, and alterations in the keratinization process, which both combine to provide a favourable environment for colonization by the bacteria Propionibacterium acnes. The bacteria secrete numerous inflammatory molecules, causing inflammation and keratinocyte
Acne vulgaris varies in severity and presentation from mild (mainly comedonal) to very severe (nodule–cystic). Treatment recommendations vary with severity of disease and include the use of topical retinoids, such as adapalene, for mild to moderate acne. While effective against acne vulgaris, many anti-acne treatments, including topical retinoids, can alter the skin barrier, causing an increase in TEWL, decreased skin hydration and skin sensitivity/irritation. Thus, acne sufferers often experience a double cause of fragile skin, from both the disease itself (pathological) and the treatment (iatrogenic). Due to the poor tolerability of these topical retinoid treatments, compliance with treatment is often low, or a moisturizing product is used in combination with treatment, which can lower treatment efficacy if poorly chosen. However, in contrast to lowering efficacy, some cosmetic products containing keratolytic agents have been shown to be effective adjunctive agents when combined with standard acne treatment regimens, and can aid with adherence to acne treatment programmes. In this study, we investigated the efficacy and tolerance of a standard topical retinoid treatment in combination with a dermo-cosmetic care product containing glycolic, lactic and salicylic acids and Rhealba® Oat Plantlets Extract, compared with the standard treatment alone, in subjects aged 15–35 years with moderate symmetrical acne vulgaris.

Materials and methods
This randomized, open-label, controlled study was carried out at a single centre in Italy between October 2015 and February 2016. The study was conducted in accordance with the ICH harmonized tripartite guidelines for Good Clinical Practice, the Declaration of Helsinki and national regulations, with written informed consent obtained from all subjects (and parents/guardians if minors) prior to enrolment in the study. The aims of the study were to evaluate the benefits and tolerance of a combination treatment of a dermo-cosmetic care product with a topical acne treatment, compared with the acne treatment alone.

Male or female subjects aged 15–35 years were included in the study if they had phototype I, II, III or IV, moderate symmetrical facial acne vulgaris with a score of 3 on the Investigator’s Global Assessment Scale (IGA) and 30–150 total lesions, of which 20–100 were non-inflammatory and 10–50 were inflammatory. Main exclusion criteria were as follows: pregnant or breastfeeding; asymmetrical acne vulgaris; more than one nodule on the face; acute, chronic or progressive disease considered incompatible with the study; facial skin disease other than acne vulgaris liable to interfere with the study assessments; hormone dysfunctions; hypersensitivity or intolerance to any cosmetic product or any component of the topical acne treatment used; excessive exposure to sunlight/UV rays within 4 weeks; use of anti-acne or anti-seborrhoeic cosmetic leave-on product within 7 days; use of systemic antibiotics, zinc gluconate, topical or hormonal acne treatment within 4 weeks; use of systemic isotretinoin within 6 months; and modification/introduction of hormonal contraception within 3 months. Subjects were asked to avoid excessive or prolonged UV exposure throughout the study, and to not wash their face for at least 4 h after product application.

Two products were used in the study: the ‘test product’, containing glycolic, lactic and salicylic acids and Rhealba® Oat Plantlets Extract (PHYS-AC Global®; A-DERMA, Lavaur, France), and the ‘associated product’, a topical retinoid acne gel containing 0.1% adapalene (Differin® 0.1% gel; Galderma Ltd, Lausanne, Switzerland). Each subject received a different treatment on each side of the face. On one side (tested side), subjects were asked to apply the associated product once daily in the evening and the test product once daily in the morning. On the other side (control side), subjects were asked to only apply the associated product once daily in the evening. Subjects were provided with a diary to record their compliance with product application schedules, any skin reactions and additional treatments. The diary also contained the subject cosmetic satisfaction questionnaire, which was completed at the end of the study period to measure the subject’s perception of the test product.

Assessments were performed independently on each side of the face at baseline (Day 1) and each of the weekly study visits (days 8, 15, 22 and 29). Efficacy evaluation included static investigator’s global assessment of acne severity (IGA) and counts of facial lesions (non-inflammatory and inflammatory). Additionally, patient’s global assessment of improvement (PGA) was measured at all visits except baseline on the following 6-point scale: 0 = much worse, 1 = minimally worse, 2 = no change, 3 = minimally improved, 4 = much improved, 5 = very much improved.

Local tolerance of the products was tested by assessment of the intensity of functional (burning sensation, warm sensation, itching, tightness, stinging) and physical (redness, desquamation, dryness) signs at each study visit, including immediately following application of the test product on Day 1. Each reported sign was graded as very mild, mild, moderate or severe by the investigator. Global tolerance was also assessed at the final study visit (Day 29) by the investigator using a 5-point scale (1 = excellent, 2 = very good, 3 = good, 4 = moderate, 5 = bad). Any adverse events (AEs), serious AEs (SAEs) and AEs leading to premature withdrawal were recorded throughout the study. Skin barrier integrity [transepidermal water loss (TEWL)], hydration index (HI) (measured by corneometry) and pH were measured independently on each side of the face at each study visit, and standardized photographs were also taken.

The sample size of 56 subjects was calculated using the SAS Proc Power procedure, with 50 subjects estimated as being required to achieve a 1 – β = 90% power with a type I error set to α = 5% (two-sided conditions), and assuming 10% of the subjects were non-assessable at the end of the study. All statistical analysis was performed on the full analysis set (FAS), that is all subjects who were enrolled in the study and received the
study treatment at least once. An ANCOVA was used to assess the difference in total number of lesions between days 29 and 1, with product and side as fixed factors, subject as a random factor and value at baseline as a covariate. The Wilcoxon test using the product (mean score 5.1) and side as fixed factors, subject as a random factor and difference in total number of lesions between days 29 and 1, with reductions in the total number of lesions, and a percentage classified as ‘almost clear’ increasing over the course of the study (from 0% on Day 1 to 6% on Day 29 for both sides).

At all post-baseline time points, mean PGA of acne improvement was higher on the tested side than the control side (Fig. 1), with significant differences at Day 8 ($P = 0.033$), Day 15 ($P = 0.003$) and Day 29 ($P = 0.043$). Figure 2a,b illustrates the differences in PGA of improvement from baseline for the tested and control sides at Day 29, for a subject who reported a ‘much improved’ PGA for the tested side. Overall, the subjects globally liked the test product, giving it a mean score of $7.5 \pm 1.7$ of 10 in the cosmetic satisfaction questionnaire. Forty-three of the 45 subjects who completed the questionnaire (95.6%) gave the test product a global score of $5$. The most commonly reported comments were that the test product was hydrating (16 subjects) and that it was easily absorbed (five subjects). Each negative comment was only reported by one subject, except that the test product was too oily (two subjects). Overall, at least 88% of subjects gave a score of $\geq 5$ to each of the product satisfaction questions included in the questionnaire, and 94% stated that they felt their skin was ‘comfortable’ immediately after application of the product (mean score $\pm$ standard deviation: 7.1 $\pm$ 1.7).

Generally, both the test and associated products were well tolerated, with very few local functional and physical signs reported at any of the study visits (Fig. 3a–f). On Day 29, a slightly higher percentage of subjects reported dryness and desquamation for the control side of the face; however, this difference was not significant. When the sum of all physical and functional signs was considered, there were significantly less signs on Day 1 after application of the test product ($P = 0.048$) and on Day 15 ($P = 0.048$) on the tested side, and a trend towards higher local tolerance throughout the study duration (Fig. 4). The test product was well tolerated in combination with the associated product. In total, at least one AE was reported for 16 subjects (28.6%). Of these, 33 AEs in 11 subjects were suspected to be related to the associated product (adapalene 0.1%) only, and eight AEs in six subjects were suspected to be at least possibly related to the test product combination (Table 2). These AEs were all classified as very mild to moderate in severity, and no treatment was required. None of the AEs were identified as being related to the test product only, and there were no SAEs or AEs leading to subject withdrawal from the study.

### Results

Of the 56 subjects who enrolled in the study, 49 (88%) completed the five study visits. Five of these subjects (9%) withdrew for personal reasons (e.g. time commitments) and the other two (3%) were lost to follow-up. Table 1 shows the demographics and baseline characteristics of the subjects. Most (86%) of the enrolled subjects were female and all had skin phototype II or III. The majority of subjects (75%) had a family history of *acne vulgaris*, and the subjects had had the condition for an average of 5.9 years. Baseline lesion counts and instrumental parameters were similar for both sides of the face.

Both the control and tested sides of the face showed a significant reduction in acne lesions by Day 29 ($P < 0.001$) compared to baseline, with reductions in the total number of lesions, and the number of non-inflammatory and inflammatory lesions of 54.1%, 53.7% and 55.2% on the tested side and 53.0%, 52.2% and 55.6% on the control side, respectively. The differences from baseline were significant for each of the study visits at $P < 0.0001$ for the tested side, and $P < 0.001$ for the control side; however, there were no significant differences observed between the tested and control sides. Similar results were observed when lesions were further stratified by type: open or closed comedones, papules, pustules, nodules.

As with the lesion counts, the tested and control sides showed very similar levels of efficacy in terms of investigator’s global assessment (IGA) during the course of the study, with the percentages of subjects with moderate disease decreasing at each study visit to Day 29 (from 100% on Day 1 to 28% on Day 29 for both sides), and the percentage classified as ‘almost clear’ increasing over the course of the study (from 0% on Day 1 to 6% on Day 29 for both sides).

Table 1  Demographics of enrolled subjects and baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) ± SD</td>
<td>22.1 ± 5.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (14.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (85.7%)</td>
</tr>
<tr>
<td>Phototype</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>II</td>
<td>12 (21.4%)</td>
</tr>
<tr>
<td>III</td>
<td>44 (78.6%)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
</tr>
<tr>
<td>Acne vulgaris</td>
<td></td>
</tr>
<tr>
<td>Number (%) with family history of <em>acne vulgaris</em></td>
<td>42 (75.0%)</td>
</tr>
<tr>
<td>Age at onset of <em>acne vulgaris</em> (years) ± SD</td>
<td>16.3 ± 3.6</td>
</tr>
<tr>
<td>Mean duration from <em>acne vulgaris</em> onset (years) ± SD</td>
<td>5.9 ± 4.3</td>
</tr>
<tr>
<td>Acne treatments within past year (N, %)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>21 (37.5%)</td>
</tr>
<tr>
<td>Topical treatments only</td>
<td>24 (42.9%)</td>
</tr>
<tr>
<td>Systemic treatments only</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Topical and systemic treatments</td>
<td>11 (19.6%)</td>
</tr>
</tbody>
</table>
There was also a trend towards higher global tolerance for the tested side, compared with the control side, but the differences were not statistically significant ($P = 0.392$). Global tolerance was assessed as ‘excellent’ for the tested side in nearly three quarters of the subjects (74.5%), compared with 68.6% for the control side (Fig. 5).

The increased hydration reported in the cosmetic satisfaction questionnaire was also demonstrated for the test product using instrumental parameters. Transepidermal water loss (TEWL) was high at baseline for both sides of the face, but the decrease from baseline level on the tested side was significantly greater than that observed for the control side over the duration of the study (Fig. 6a). There was no significant change in TEWL over the 4-week study duration for the control side ($P = 0.722$), whereas there was a significant decrease for the tested side ($P = 0.029$). Similarly, as shown in Fig. 6b, the change in hydration index from baseline measurements was significantly higher throughout the study for the tested side compared with the control side (Day 8: $P = 0.001$, Day 15: $P = 0.007$, Day 22: $P = 0.003$, Day 29: $P = 0.0005$), and overall, there was a significant increase in hydration index for the tested side over the 4-week period ($P = 0.0008$), which was not observed for the control side ($P = 0.178$). No significant differences in change in pH from baseline were observed between the tested and control sides during the study ($P = 0.952$).

**Discussion**

In this study, the combination of the test product containing glycolic, lactic and salicylic acids and Rhealba® Oat Plantlets Extract and adapalene 0.1% treatment resulted in increased skin hydration and patient global assessment than adapalene alone, with no observed impact on efficacy. The hydrating properties reported by subjects were confirmed with two independent instrumental measurements, which showed a reduction in TEWL and higher HI for the tested side, compared with the control side at all time points in the study. The addition of the acidic test product did not alter skin pH and was well tolerated despite containing high levels of alpha- and beta-hydroxy acids.

Topical retinoids have been reported to cause mild skin irritation, and due to the high levels of troublesome side-effects from acne treatments, patients often use over-the-counter moisturizers to counteract dryness and irritation. Some moisturizing products have been shown to interfere with the efficacy of these topical treatments; however, non-comedogenic cosmetic products containing no irritant ingredients can reduce the negative effects of the retinoid treatments without compromising effectiveness. As the tested product contained a high concentration of acids (9% total) and an acid pH (3.5), it could be expected that there would be disruption of the skin barrier when associated with a topical retinoid and an increased risk of adverse reactions, particularly tingling, stinging, erythema, burning, pruritus or dryness, which have previously been observed for this class of alpha-hydroxy acids. However, the results of our study demonstrated the opposite, with increased skin hydration and a reduction in physical and functional signs. Similarly, no increase in irritation was observed, and although not statistically significant, fewer subjects reported dryness on the tested side than on the control side. Both the test and control treatments were well-tolerated.
tolerated, and functional and physical signs were generally fewer than reported in phase III clinical trials; however, the treatment period in those trials was much longer (12 weeks compared with 4 weeks in the current study). The test product contained Rhealba® Oat Plantlets Extract, which is frequently used to aid in restoration of the epidermal barrier. It has also been shown to have anti-inflammatory properties, by inhibiting the inflammatory pathway, which may be why it is seen as effective in management of reactive skin in skin disorders such as acne vulgaris. The inclusion of this extract counteracts the irritating properties of the hydroxy acids, resulting in a lessening of the pathogenic and iatrogenic fragile skin conditions in these subjects. TEWL measurements were high at baseline in our study, indicating that disruption to the epidermal barrier had occurred in these subjects with moderate acne. The improved hydration associated with use of the dermo-cosmetic product was confirmed by TEWL and HI measures, and could aid in increasing compliance to acne treatments, which are often discontinued due to the poor tolerability of the products. Previous studies have shown an increase in compliance when

![Illustrative photographs at baseline and on Day 29 (Week 4) for one subject for (a) the control side and (b) the tested side. The control side was given a PGA of 0 (no change) and the tested side a PGA of 2 (much improved) on Day 29.](image-url)
Figure 3  Percentage of subjects reporting functional (a–c) and physical signs (d–f) for the tested and control sides, on each of the study visit days. Data are not shown for tightness and stinging as no subjects reported these signs after treatment.

Figure 4  Mean (±SE) sum of all functional and physical signs at each study visit. Significant differences between the tested and control sides are indicated, where *P < 0.05.
Adapalene was administered with a moisturizer. A recent study by de Lucas and colleagues showed that adherers to adjuvant treatment were significantly more likely to adhere to the topical retinoid treatment, which in turn was associated with a significant reduction in acne severity. In our study, the potential for increased compliance was also supported by the patient assessments and satisfaction questionnaires. The efficacy results for the topical retinoid treatment investigated in this study are higher than those observed previously in randomized clinical trials in which adapalene 0.1% was applied daily. The decrease in lesion count observed in our study is similar to those observed after 12 weeks of treatment with adapalene 0.1% gel in previous studies. This observed increase in efficacy may be at least in part explained by high levels of adherence to the treatment schedule, due to the short study length (4 weeks) and regular follow-up sessions (every week). The similarities in efficacy between the tested and control sides indicated that there was no interference of the tested dermo-cosmetic product with treatment efficacy. Although it may have been expected that the association of the two products would lead to better efficacy for the tested side, this was not observed during the study in terms of lesion counts or IGA severity assessment. This may be at least partially influenced by the short study period, which was limited by the complexity of the split-face design of the study, the high rates of adherence to both the control and test treatments and the small sample size. The differences in PGA seen between the control and tested sides indicate that there was at least a perception of better results amongst the subjects from the combination of adapalene and the dermo-cosmetic product, even if no physical differences in outcome from the test and control treatments were observed by the investigator.

This is a small-scale study on patients with moderate acne vulgaris. While showing promising results for decreasing some of the negative side-effects associated with acne therapy, the impact on mild or more severe forms of acne is yet to be assessed. However, this study shows a clear potential benefit of the use of this dermo-cosmetic care product containing glycolic, lactic and salicylic acids and Rhealba Oat Plantlets Extract in association with the retinoid-based topical acne treatment, for improved management of moderate acne vulgaris by reducing possible adverse reactions, increasing skin hydration and restoring barrier function.

Table 2  Adverse events (AEs) suspected to be at least possibly related to the test product and associated product combination. AEs which were unlikely to be related or not clearly attributable are also included as an association with the product combination could not be ruled out.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Maximal severity of event</th>
<th>Duration (days)</th>
<th>Causality of the combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning sensation</td>
<td>Very mild</td>
<td>8</td>
<td>Likely</td>
</tr>
<tr>
<td>Worsening of acne</td>
<td>Mild</td>
<td>14</td>
<td>Not clearly attributable</td>
</tr>
<tr>
<td>Worsening of acne</td>
<td>Mild</td>
<td>15</td>
<td>Not clearly attributable</td>
</tr>
<tr>
<td>Desquamation</td>
<td>Mild</td>
<td>8</td>
<td>Likely</td>
</tr>
<tr>
<td>Redness</td>
<td>Mild</td>
<td>8</td>
<td>Likely</td>
</tr>
<tr>
<td>Dryness</td>
<td>Very mild</td>
<td>8</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>Very mild</td>
<td>Unknown</td>
<td>Not clearly attributable</td>
</tr>
<tr>
<td>Hyperseborrhoea</td>
<td>Moderate</td>
<td>4</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

Figure 5  Global tolerance of the tested combination and control products, assessed at Day 29.
Clinical study on lesional skin

A dermo-cosmetic containing Cicahyalumide® is well tolerated and improves healing in a laser ablation model of skin damage

A variety of dermatological procedures aim at resurfacing the skin by removing the stratum corneum and sometimes further layers of the epidermis. Chemical peels, which use chemicals to induce accelerated shedding or necrosis of cells in the epidermis, are probably the most frequent skin resurfacing procedures employed by dermatologists worldwide. Continuous-wave ablative CO2 lasers were first used for resurfacing but have been replaced by fractional CO2 and non-ablative pulsed-dye lasers (PDLs) because they remove the epidermis and part of the dermis, which can result in long recovery times and scarring. Intense pulsed light (IPL), which uses xenon flash lamps applied directly to the skin, is another non-ablative light therapy now frequently used for treating superficial skin lesions and hair removal. PDL and IPL work by selective photothermolysis, which was developed in the early 1980s for the targeted damage of pigmented structures, cells and organelles. The principle behind selective thermolysis is that emitted light is absorbed by pigmented structures, such as oxyhaemoglobin, and released as heat, damaging the targeted structures without affecting nearby tissues or structures. Dermal needling or micro-needling using handheld devices, such as a Dermaroller®, is also becoming increasingly popular to treat scars, such as in acne vulgaris, and works by stimulating the production of new connective tissue beneath the scar. Dermabrasion, which involves physical removal of skin surfaces with an abrasive surface, has largely been supplanted by these methods.

Although superficial peels, PDL, IPL and dermal needling are considered to be well tolerated and safe, they can induce an inflammatory response, transient sensitivity and other undesirable effects. By removing or damaging the stratum corneum and possibly additional layers of the skin, resurfacing techniques temporarily disrupt the skin’s barrier function, leaving the skin fragile, permeable and often irritated. This can also make the skin sensitive to topical products and patients susceptible to irritant contact dermatitis. Accordingly, skincare products are frequently proposed by dermatologists for patients who have had aesthetic resurfacing procedures.

Epitheliale AH DUO® (A-DERMA Laboratories, Lavaur, France) is a fragrance- and dye-free oil-in-water-based cream formulated to soothe and heal damaged skin. This cream contains Cicahyalumide®, a mixture of three key active components: Rhealba®, a protein-free oat plantlet extract; the dipeptide L-Ala-L-Glu; and hyaluronic acid. These components, combined with the cream base, reduce inflammation, promote healing, moisturize the skin and help restore the skin’s barrier function. Here, we describe the efficacy and tolerability of Epitheliale AH DUO® for promoting healing in a laser ablation model of skin damage.

Materials and methods

Study design Efficacy was assessed in an intra-individual randomized controlled study carried out at proDERM Institute for Applied Dermatological Research (Schenefeld/Hamburg, Germany) between January and February, 2015. The primary objective was to compare the time to re-epidermization in Er-YAG laser-ablated skin treated with Epitheliale AH DUO® (test
product; A-DERMA Laboratories, Lavaur, France), reference product (Epitheliale AH®; A-DERMA Laboratories), an active comparator containing resveratrol–copper complex (Cicabio®; Bioderma International, Lyon, France) or no treatment.

**Ethics** The study was approved by the Independent Ethics Committee of Freiburg, Germany, and was conducted in accordance with the Declaration of Helsinki (1964) and its subsequent revisions. All participants provided written, informed consent.

**Participants** The study included healthy volunteers 18–45 years of age with Fitzpatrick skin type I, II or III. To meet internal requirements for efficacy evaluation, the study was planned to include at least 20 participants. All participants had to have had a tetanus vaccination within 10 years. Participants could not be infected with human immunodeficiency virus or hepatitis; have allergy or contact dermatitis provoked by one of the ingredients in the test product; have dermatological lesions on the inner aspect of the forearm; have a scarring pathology; suffer from congenital methaemoglobinemia or porphyria; or have any chronic disease or pathology likely to influence the study outcome according to the investigator. Participants could not be taking oral or systemic corticosteroids within 4 weeks before inclusion; oral or systemic non-steroidal anti-inflammatory treatments within 7 days before inclusion; agents causing diuresis within 2 months before inclusion; anticoagulants with 1 week before inclusion; or any treatment liable to induce methaemoglobinemia 2 weeks before inclusion. Participants could also not be using any cosmetic product on the inner aspect of the forearm other than personal hygiene products within 1 week before inclusion: keratolytic, exfoliant, emollient or self-tanning products on the inner aspect of the forearm within 2 weeks before inclusion; or personal hygiene products to the inner aspect of the forearm the evening before inclusion. Women could not be pregnant or breastfeeding.

**Study conduct** Four 10 × 10 mm square epidermal ablations were made with an Er-YAG laser on the inside surface of the upper forearms of volunteers under local anaesthesia as previously described.19 Briefly, the skin was anesthetized using AnesdermGe® (Pierre Fabre, Lavaur), disinfected with Cutasept® (Paul Harmann AG, Heidenheim, Germany) and irradiated with a SMART 2940 + Er-YAG laser (DEKA, Calenzano, Italy) to create the ablations.

For each subject, the ablations were randomized 1 : 1 : 1 : 1 to receive ~8 mg of test product, ~8 mg of reference product, ~8 mg of active comparator or no product. Ablated zones receiving a product were treated once daily for 6 days by trained technicians. At each visit, a fresh semi-occlusive patch was applied to prevent contact of the wounds with clothing. From Day 7 to the end of the study, products were applied by participants twice daily, with a delay of 8–12 h between applications. The study was open-label for ablations receiving no product and double-blind for ablations receiving a product.

**Outcome measures** The primary outcome measure was the time to wound closure, calculated from the wound surface area measured on colour-calibrated standardized digital photographs. Photographs were taken using an EOS 5D Mark II digital camera (Canon, Tokyo, Japan) fitted with a DERMLite™ Foto dermatoscope (3Gen Inc., San Juan Capistrano, CA, USA). The time to wound closure was the minimum time to obtain total re-epidermization or disappearance of the wound (when the wound surface was equal to 0). Secondary efficacy outcome measures included were the rate of wound closure; the quality of wound healing measured with a dermaTOP sensor (Eotech, Ann Arbor, MI, USA) and on a 10-point scale (from 1 for very bad to 10 for very good); and the time and rate of restoration of barrier function as measured by Tewl using an Aquaflex (Biox, London, UK). In addition, specific signs and symptoms recorded by the expert evaluator (peri-lesional erythema and oedema) and by the study volunteers (itching, burning, tension and pain) using a 4-point scale (0 = symptom not detected, 0.5 = very mild, 1 = mild, 2 = moderate, 3 = severe). Overall tolerability was assessed by the expert evaluator on a 4-point global scale (1 = very good, 2 = good, 3 = moderate, 4 = poor).

**Statistical analysis** Efficacy was assessed in the full analysis set, defined as all participants for whom at least the primary outcome measure was available. The primary efficacy analysis was comparison of the time until disappearance of the wound by a blinded analysis of high-definition, standardized digital photographs. Wound disappearance was defined as the first time where the re-epidermization surface area was 0. Secondary efficacy analyses included comparisons of the rate of the disappearance of the wound, Tewl, the rate of skin barrier restoration, re-epidermization quality and the quality of wound healing. All comparisons were made by analysis of variance with product as fixed factor and subject as random factor. Missing data were not replaced. A P-value below 0.05 was considered to indicate statistical significance.

**Results**

**Participants** The study included seven men and 15 women (aged 20–45 years, mean 33.9 ± 7.9 years) with normal skin and was conducted between 26 January and 16 February 2015. Twenty-one participants completed the study. One participant did not complete the study because of a reaction to the laser treatment the same day that was not considered to be product-related.

**Wound healing** Wound surface area measurement showed that complete wound closure occurred sooner with the test product
(12.5 ± 3.1 days) than for the reference product (14.3 ± 2.0 days; \( P = 0.0481 \)), the active comparator (17.6 ± 3.5 days; \( P < 0.0001 \)) or no product (19.0 ± 3.1 days; \( P < 0.0001 \); Fig. 7 and Table 1). Similarly, complete healing for at least 50% of subjects occurred earlier with the test product (12 days) than for the reference product (15 days), the active comparator (15 days) or no product (19 days). The rate of wound closure between days 2 and 6 did not significantly differ between any of the products and the untreated control, whereas the rate was significantly faster for test product than for active comparator or no product between days 6 and 12 (Table 3).

Restoration of skin barrier function was assessed as the decrease in TEWL (Fig. 8). Between days 2 and 6 and also between days 6 and 12, skin barrier function was restored significantly more quickly with test product than with active comparator or no product (Table 3). In addition, the TEWL at wound closure was significantly lower with test product that for no product.

In agreement with this, at all times, the evaluator considered the quality of the wound to be significantly better when the test product was applied than when the active comparator or no product was applied (Fig. 9). Qualitatively, skin quality was returned to normal at the end of the study in the zone receiving the test and reference products but not in the zones receiving the active comparator or no product (Fig. 10). Finally, at Day 12, change in skin relief from day 1 was significantly greater for the test product than for the reference product or no product, but differences were not significant at Day 15, 19 or 22 (data not shown).

**Tolerability and safety** According to the blinded evaluator, peri-lesional erythema resolved faster for the test and reference products than for the active comparator or no product (Fig. 11). Also, according to participants, itching and burning resolved faster for the test and reference products than for the active comparator or no product. Scores for tightening and pain were low and did not appear to differ between the different treatments. No oedema was detected. Finally, tolerability was considered to be very good for all participants and did not appear to differ between products.

Adverse events were reported for nine participants, none of which was considered to be related to a product. All adverse events were transient and none were considered a serious adverse event.

**Discussion**

Here, we show that the Epitheliale AH DUO®, a fragrance- and dye-free oil-in-water-based cream, is well tolerated and improves

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**Figure 7** Re-epidermization of Er-YAG laser ablations.

**Table 3** Efficacy for different products applied to Er-YAG laser ablations

<table>
<thead>
<tr>
<th>Measure</th>
<th>Test product</th>
<th>Reference product</th>
<th>Active comparator</th>
<th>No product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to complete wound closure (days), mean ± SD</td>
<td>12.5 ± 3.1</td>
<td>14.3 ± 2.0</td>
<td>17.6 ± 3.5</td>
<td>19.0 ± 3.1</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.0481</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Time to 50% of participants with complete wound closure (days)</td>
<td>12</td>
<td>15</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Rate of decrease of wound area, Day 2 to Day 6 (mm²/day), mean ± SD</td>
<td>–6.7 ± 1.3</td>
<td>–6.5 ± 2.1</td>
<td>–6.8 ± 2</td>
<td>–5.8 ± 1.8</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.62</td>
<td>0.92</td>
<td>0.0545</td>
<td></td>
</tr>
<tr>
<td>Rate of decrease of wound area, Day 6 to Day 12 (mm²/day), mean ± SD</td>
<td>–3.3 ± 0.8</td>
<td>–3.3 ± 0.9</td>
<td>–3.9 ± 0.9</td>
<td>–4.2 ± 0.6</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.96</td>
<td>0.0042</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>TEWL at wound closure (g/m²h), mean ± SD</td>
<td>23.0 ± 8.0</td>
<td>23.7 ± 6.0</td>
<td>31.0 ± 15.5</td>
<td>36.0 ± 16.6</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.87</td>
<td>0.07</td>
<td>0.0021</td>
<td></td>
</tr>
<tr>
<td>Decrease in mean TEWL, Day 2–12</td>
<td>–77%</td>
<td>–76%</td>
<td>–69%</td>
<td>–69%</td>
</tr>
<tr>
<td>Rate of decrease of TEWL, Day 2–6 (g/m²h/day), mean ± SD</td>
<td>–11.0 ± 6.0</td>
<td>–12.1 ± 3.8</td>
<td>–5.6 ± 7.0</td>
<td>–4.13 ± 7.2</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.53</td>
<td>0.0017</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Rate of decrease of TEWL, Day 6–12 (g/m²h/day), mean ± SD</td>
<td>–1.5 ± 1.5</td>
<td>1.3 ± 0.7</td>
<td>2.6 ± 1.9</td>
<td>3.2 ± 1.9</td>
</tr>
<tr>
<td>( P ) vs. test product</td>
<td>0.53</td>
<td>0.0116</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; TEWL, transepidermal water loss.
healing in a laser ablation model of physical skin damage. Application of the product led to faster healing, faster cutaneous barrier restoration and better quality of healing than either no treatment or an active control cream. As expected with the wounds and with product applied to de-epidermized skin, some irritation was detected in all treatment zones; however, the test cream resulted in less undesirable effects than the active control product. Tolerability of the test product was considered to be very good, and no adverse events were considered to be related to its use.

We previously established the laser ablation model of physical skin damage to allow for robust, controlled assessments of topical treatments for wound healing. Compared to other skin wound models, such as suction blisters, abrasion, burning with a brass block or split-thickness skin graft donor sites, this model provides lesions that are less painful for the participant, easier to generate and, importantly, produce lesions of reproducible size and depth. This simplifies assessing wound healing and making comparisons between different treatments.

We previously used this model to compare a cream containing Rhealba® Oat Extract and hyaluronic acid with the same active comparator as in the current study, no treatment and a reference product containing panthenol and madecassoside. As in the current study, 21 adults were included, which, because of the intra-individual randomized design, was enough to detect statistically significant and clinical meaningful differences in wound healing, the primary outcome measure. Like the current study, the previous study showed that wound healing was faster with the test product than with the active comparator but similar to the reference product. Also, barrier recovery, as measured by TEWL, was faster for the test product than no product, although, unlike in this study, it was no faster for the test product than the active comparator.

The ability of the products in this study to improve wound healing may be due in part to the vehicle. Topical creams and emollients are known to improve barrier function and reduce skin inflammation and fragility, although most studies have been performed in patients with atopic dermatitis or other skin diseases. A few studies in healthy adults have shown that application of moisturizers or barrier creams improves TEWL after barrier disruption by sodium lauryl sulphate or tape stripping. Relatively little is known about the effects of specific topical agents or ingredients on cutaneous wound healing. Improved cutaneous healing has been reported for an aloe vera-containing...
cream applied to split-thickness skin graft donor sites, a 2% grape seed extract applied to postdermatologic surgery wounds and Symphytum herb extract applied to abrasions. Other topical agents that may accelerate cutaneous wound healing include honey, growth factors, MEBO botanical ointment and RGD peptide, although most of these have been studied in patients with burn wounds and study quality has varied widely.

The fact that test product was more effective at improving healing than the active comparator indicates that the healing effect may be due not only to the vehicle but also, possibly, to the active agents, which include Rhealba Oat Extract and hyaluronic acid. Rhealba Oat is a protein-free extract from oat plantlets that is rich in saponins and anti-inflammatory flavonoids. These can inhibit the production of inflammatory mediators, decrease the expression and action of histocompatibility complex class II molecules on dendritic cells, stimulate keratinocyte proliferation and enhance the production of extracellular matrix and cell membrane components in vitro. Hyaluronic acid is a natural component of skin and other tissues that improves wound healing, possibly by enhancing keratinocyte proliferation and migration. Thus, although the current study did not assess mechanism, we suspect that the healing effect of the test product was due to the physical properties of the vehicle cream combined with the cellular actions of the active agents in the epidermis.

Skincare products are frequently recommended for patients who have had aesthetic resurfacing procedures such as chemical peels, PDL or IPL. Resurfacing techniques temporarily disrupt the skin’s barrier function, leaving the skin fragile, permeable, often irritated and sensitive to topical products. The results of this study suggest that Epitheliale AH DUO can be safely used to speed the healing of skin wounded by resurfacing procedures or other physical damage.

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References
6 Al Hammadi A, Niarra RY, Le Mauff A, Saint Aroman M. Fragility of epidermis: epidemiology study in Middle East population, focus on United