Eur J Dermatol 2025; 35(6): 508-518

Helena POLENA[1]*
Sylvie CALLEJON[2]*
Marie SALVERT[1]
Elise ABRIC[1]
Armonie BUISSON[1]
Benoît CADARS[1]
Félix GIRAUD[2]
Julie SCALIA[2]
Noëlle REMOUE[1]
Nathalie ARDIET[1]
Michèle SAYAG[1]
Sandra TROMPEZINSKI[2]
Elodie PRESTAT-MARQUIS[1]
Brigitte DRENO[3]
Christelle GRAIZEAU[2]

*These authors contributed equally
[1]NAOS Ecobiology Compagny (Bioderma), Research and Development Department, 13290 Aix-en-Provence, France
[2]Institut NAOS des Sciences de la Vie, 13290 Aix-en-Provence, France
[3]Université de Nantes, INSERM, CNRS, Immunology and New Concepts in ImmunoTherapy, INCIT, UMR 1302/EMR6001, 44200 Nantes, France

Reprints: Noëlle Remoué <noelle.remoue@naos.com>

Article accepted on 26/08/2025

An innovative ecobiological wound repair cream that restores the microbiome

Background: Small everyday wounds would benefit from optimal healing conditions, and the role of the microbiome in this process is being increasingly discussed. *Objectives:* To evaluate a wound repair cream (Cicabio Crème+, NAOS Ecobiology Company, Bioderma, France), assessing its effects on the skin microbiome and wound healing. *Materials & Methods:* The impact on the microbiome was evaluated by monitoring restoration of diversity after disinfection. The efficacy of the repair complex was assessed *ex vivo* using a 3D wound-healing human skin model to analyse closure and protein expression. Short-term evaluation of adherence, gas permeability, wound protection, and hydration was assessed. *In vivo* efficacy was examined through two clinical studies: one on healing erosive areas and another after chemical peel. *Results:* After disinfection, the cream accelerated restoration of microbiome diversity (+31%, p=0.001) without promoting pathogenic/commensal bacteria or altering the level of *Staphylococcus epidermidis* (p=0.193). In a 3D wound-healing model, the repair complex enhanced wound closure, promoting protein expression (Ki67, loricrin, CD44, collagen XVII, VII, III) and re-epithelialisation. The cream adhered to the skin, allowed gas exchange, and provided protection and hydration. *In vivo*, the cream reduced transepidermal water loss (day 4: p=0.016; day 7: p=0.014), erythema (day 7: p=0.023), and functional signs (day 4: p=0.032) of erosive wounds. Following chemical peels, the cream reduced inflammation (day 7: p=0.037), visible damage (day 7: p=0.029), and skin pH (day 1: p<0.001). *Conclusion:* We demonstrate, for the first time, protection of microbiome diversity, stimulation of wound closure, and preservation of skin pH using a wound repair cream.

Key words: wound healing, 3D skin model, microbiome, clinical evaluation, chemical peel

Small, everyday wounds are often left untreated, increasing the risk of infection, sustained inflammation, delayed wound closure, and poor scarring [1]. Although most of these wounds spontaneously heal, it is important to foster natural repair mechanisms.

The restoration of skin integrity is achieved through four interconnected stages: haemostasis, inflammation, proliferation, and tissue remodelling. These stages involve several cell types whose activities are regulated by numerous mediators [2-4]. Among the external factors that positively influence this process, a humid environment is well-documented [5, 6]. Consequently, dedicated semi-occlusive, protective cosmetics or topical medical devices have been developed, providing faster healing and improving scar outcomes [7-11].

There is growing evidence that the skin's commensal microbiome, particularly *Staphylococcus epidermidis*, contributes to wound healing [12-14]. It helps prevent pathogen overgrowth by stimulating innate defences, bacterial interference, and the production of antimicrobial compounds [14]. Importantly, commensal bacteria influence immunological pathways, inducing CD8+ T cells and IL-1β signalling, both of which contribute to skin regeneration and re-epithelialisation [13]. They also contribute to skin barrier homeostasis by participating in ceramide synthesis in a symbiotic process that also promotes bacterial colonisation [15]. Thus, preserving the skin's resident microbiome is essential, and current guidelines recommend avoiding disinfection of uninfected wounds [16].

Thus, a wound repair cream dedicated to acute wounds should protect the skin microbiome, provide a protective environment against infections and further traumas, preserve and promote the skin's repair mechanisms, and have soothing properties to prevent itching and scratching that could delay healing. Following the principles of ecobiology, to promote skin health by maintaining or restoring its equilibrium [17, 18], we have

doi:10.1684/ejd.2025.4979

To cite this article: Polena H, Callejon S, Salvert M, Abric E, Buisson A, Cadars B, Giraud F, Scalia J, Remoue N, Ardiet N, Sayag M, Trompezinski S, Prestat-Marquis E, Dreno B, Graizeau C. An innovative ecobiological wound repair cream that restores the microbiome. *Eur J Dermatol* 2025; 35(6): 508-518 doi:10.1684/ejd.2025.4979

formulated a wound repair cream that fosters conditions conducive to healing and preserves the skin microbiome. We assessed its effects on the skin microbiome, wound healing, and recovery following a minimally invasive chemical peel procedure.

Materials and methods

Investigated product

The investigated product was a wound repair cream (Cicabio Crème+, NAOS, LABORATOIRE BIODERMA, France). The composition of the wound repair cream and the placebo cream used in the post-peeling study, as well as the active ingredient of the repair complex used in experiments with the 3D wound-healing model, are presented in *table 1*.

Analysis of skin microbiome diversity

To assess the effect of the wound repair cream on the restoration of microbiome diversity, the skin on the back of 20 Caucasian females (aged 23-50) was disinfected with 70% ethanol, rinsed with nuclease-free water, and air-dried. Bacterial samples were collected before, and five minutes and three hours after disinfection, and results from a skin zone (5 cm^2) to which the cream was applied after disinfection (1.5 µL/cm^2) were compared to those of an adjacent untreated area.

After bacterial genomic DNA extraction (TRIzol™, Thermo Fisher Scientific, USA), microbiome diversity was analysed by next-generation high-throughput sequencing of the V3-V4 variable regions of the 16S rRNA gene [19]. The procedure included cross-contamination prevention measures, a positive control (artificial bacterial community "ABC control"), and a negative control for the complete library preparation process. Diversity was assessed by calculating the Shannon index and the number of operational taxonomic units (OTU). The relative abundance of the skin microbiome's 10 most frequent bacterial genera was also determined. Results were compared by calculating the Bray-Curtis dissimilarity index using data before disinfection as a reference.

The presence of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Staphylococcus hominis* was evaluated by qPCR using species-specific primers and SsoAdvanced™ PreAmp Supermix (BIO-RAD, USA). Results from PCR reactions were calibrated with different dilutions of reference strains to calculate the number of colony-forming units (CFU)/sample.

Table 1. List of ingredients of the wound repair cream evaluated and their properties.

Ingredients (INCI names)	Properties
Aqua/water/eau°	Medium
Glycerine* Butylene glycol* Pentylene glycol 1,2-hexanediol Caprylyl glycol	Hydration
Xylose°* Sodium hyaluronate°* Sodium polyglutamate°*	Repair (patented complex)
Acetyl dipeptide-1 cetyl ester*	Reduction in skin hypersensitivity
Triglyceride* Caprylic / capric triglyceride Ethylhexyl palmitate* *Brassica campestris* (rapeseed) seed oil Hydrogenated rapeseed oil *Simmondsia chinensis* (Jojoba) seed oil* Squalane* *Helianthus annuus* (sunflower) seed oil	Restructuring
Polyglyceryl-3 polyricinoleate Tapioca starch Polyglyceryl-3 diisostearate Magnesium sulfate Sodium citrate Xanthan gum Tocopherol Citric acid Fructooligosaccharides* Mannitol* Rhamnose* Xylitol*	Cream base (texturing and protection)

°*Active ingredient of the repair complex.*
**Ingredients absent in the placebo cream used for the post-peeling efficacy study.*

Evaluation of wound healing in a skin model

Analysis was performed using a 3D wound-healing model (LabSkin, France), consisting of a mature human skin equivalent with a 3-mm full-thickness punch wound, deposited onto a dermal layer supporting cell migration. Daily topical applications of the repair complex (15 µL), epidermal growth factor (a mitogenic polypeptide known to stimulate wound healing [20], as a positive control) (0.05 mg/mL in PBS buffer), or PBS buffer (negative control) were added 24 hours post-injury.

The wound surface was assessed by analysing dividing basal keratinocytes and epidermal terminal differentiation using, respectively, cytokeratin-14 and involucrin primary antibodies (Abcam, UK). Both were evaluated using Alexa Fluor®-conjugated secondary antibodies (Molecular Probes, USA). Samples were visualised using a Leica LSM 880 confocal microscope and analysed using Image J software.

Re-epithelialisation was evaluated on cross-sections of model wound-healing skin embedded in OCT and stained with haematoxylin-phloxine-saffron.

Finally, the expression of marker genes was analysed on paraffin-embedded sections, labelled with primary antibodies against the cell proliferation marker Ki67 (Dako, USA), the epidermal terminal differentiation marker loricrin (Abcam, UK), the hyaluronic acid receptor CD44 (Santa Cruz Biotechnology, USA), the dermal-epidermal junction markers type VII collagen (Dako, USA) and type XVII collagen (Abcam, UK), and the dermal marker type III collagen (Novotec, France). After detection with Alexa Fluor® 568-conjugated secondary antibodies, samples were acquired (Zeiss AxioScan.Z1 slide scanner), and two images per independent skin model and condition were analysed using Zen software.

In vivo evaluation of short-term effects of the wound repair cream

Short-term properties of the wound repair cream were investigated through non-invasive clinical studies conducted on healthy Caucasian females, aged 18-70. In all these studies, untreated skin zones were used as references.

The cream's adherence to the skin was evaluated by assessing its occlusive effect. This evaluation relied on the quantification of transepidermal water losses (TEWL), the minute loss of body water through the skin. Upon application of a water-impermeable cream (occlusive effect), TEWL is reduced and if the cream adheres to the skin, this reduction should persist even after an attempt to remove the product. Therefore, we compared TEWL levels (using a Tewameter TM HEX®, Courage+Khazaka electronic GmbH, Germany) measured just before cream application (4 µl/cm^2) and 15 minutes later, following an attempt to remove the cream using blotting paper and applying a standardised strong pressure. This assessment was conducted on the inner forearm of 10 healthy Caucasian female volunteers, all of whom exhibited relatively high baseline TEWL (>7 g/m^2/h).

Transcutaneous gas permeability was analysed by 30-minute-long measurements of O_2/CO_2 partial pressure using a TCM5 FLEX monitor (Radiometer, France). Measurements (n=21; Caucasian females) were performed before and 30 minutes after a 2 µL/cm^2 cream application onto an area from the volar side of a forearm. Additional measures were performed two and seven hours later. Results were compared to those of the equivalent untreated area from the second forearm. Due to aberrant measurements for one subject, only 20 subjects were analysed, 30 minutes after cream application.

Another property assessed was protection against friction, evaluated on 10 Caucasian females. After initial TEWL quantification (using a Tewameter TM HEX®, Courage+Khazaka electronic GmbH, Germany), 2 µL/cm^2 of cream was applied onto the inner forearm. After cream penetration, the treated zone was rubbed for 45 seconds with fine sandpaper. After 15 minutes, TEWL was measured, and the skin was rubbed again. A final TEWL quantification was made 15 minutes later. Results from the cream-treated area were compared to those of a similar region of the other forearm subjected to rubbing but without cream application.

The hydrating property of the cream was evaluated on a randomly selected forearm of 10 Caucasian females by measuring skin hydration at various time points. Skin hydration was measured using a Corneometer® CM 825 (Courage+Khazaka electronic GmbH, Germany), which quantifies the capacitance of the stratum corneum, primarily influenced by its water content as it is the constituent with the highest di-electrical constant within the skin. Results from a skin area onto which 1 µL/cm^2 of cream was applied were compared to those of an untreated equivalent zone. Skin hydration measurements were performed before cream application, as well as 1, 3, 6 and 8 hours after the cream was applied. All measurements were conducted after 15 minutes of acclimation to standardised conditions, and the cream was wiped off the subjects' forearms with a clean absorbent paper before the one-hour time point.

Finally, the humectant property of the cream was assessed by measuring the thickness of the stratum corneum and the living epidermis using Line-field Confocal Optical Coherence Tomography (deepLive™ OSP11, DAMAE Medical, France). Evaluations were performed on 23 Caucasian females, comparing results from an area of the dorsal face of one hand that received a 4 µL/cm^2 application of cream to those of an equivalent untreated area on the other hand. Measures were performed before cream application as well as 30 minutes and one hour later. As the skin zone for these two later time points was different, their baseline characteristics were evaluated separately. Automatic segmentation of the images acquired enabled calculation of the thickness of the stratum corneum and the living epidermis.

Clinical assessment of the healing of erosive areas

Standardised erosive areas (1 cm diameter) were generated by mechanical brushing of the inner forearm skin of 24 subjects (aged 19-55). One erosive area of a subject was randomly allocated to the wound repair cream (equivalent to the size of a hazelnut per application), while the other remained untreated. From day 1 to 7, erosive areas received one cream application daily and were covered with a semi-occlusive dressing (Smith & Nephew, UK). From day 8 to 14, erosive areas remained uncovered, and treated areas received twice-daily cream applications.

TEWL measurements and assessor-blind clinical evaluations of lesions were performed on days 3, 4, 7, and 14. Assessors scored erythema (0: none to 4: very strong) and crust coverage (0: none to 3: crust on the entire lesion). Subjects also reported sensations of lesions (burning, tingling, and itching; each scored on a 0 [none] to 3 [strong] scale) and each of these scores was combined into a functional sign score.

Clinical evaluation of recovery from a chemical peel

The repairing and soothing effects of the wound repair cream after a 70% glycolic acid facial peel (General Topics SRL, Italy) were evaluated in a split-face comparative, randomised, double-blind study conducted under dermatological control (n=22; Caucasian females, aged 26-45). One randomly selected hemiface received applications of the cream twice a day, starting immediately after the peel procedure. Results were compared to those of the placebo treatment on the second hemiface. Assessments were performed immediately after the peel and on days 1, 2, 3, 7, and 14.

A dermatologist scored individual parameters using a 0 (absent) to 4 (very severe) scale. An inflammation severity score was based on the combination of skin redness and oedema. A skin damage score was based on post-inflammatory pigmentation, sequelae telangiectasia, crusts, residual redness, and desquamation. Subjects rated pain and itching, which were combined to form a functional sign score. Finally, all scores were combined into a global composite score. Additionally, cheek skin pH was measured at each time point. Product tolerance was monitored throughout the study.

Statistical analysis

Results are presented as mean ± standard error of the mean (SEM) and data distribution was assessed with Shapiro-Wilk tests (α=0.01). Microbiome diversity was analysed using Wilcoxon signed-rank tests and the Bray-Curtis dissimilarity index. Results from the short-term evaluations were analysed using paired t-tests or ANOVA followed by Tukey HSD. Results from the clinical evaluation of the healing of erosive areas and the recovery after a chemical peel were compared using Wilcoxon signed-rank tests or Kruskal-Wallis tests with *post hoc* Dunn's tests.

Results

Effect of the wound repair cream on the skin microbiome

We first examined how the wound repair cream could help restore microbiome diversity after disinfection. Analysis of both diversity indexes, the Shannon index and the number of Operational Taxonomic Units (OTU), yielded similar results (*figure 1A, B*). Disinfection significantly reduced diversity (Shannon index: -56%, p<0.001; OTU: -35%, p=0.012). The two indexes remained similar in untreated skin three hours after disinfection (Shannon index: p=0.368; OTU: p=0.295). A single cream application significantly increased diversity after three hours, surpassing diversity after disinfection (Shannon index: +31%, p=0.001; OTU: +63%, p<0.001) and that of untreated areas after three hours (Shannon index: +32%, p=0.017; OTU: +49%, p<0.001). These results were confirmed when assessing the relative abundance of the 10 most frequent genera of the skin microbiome (*figure 1C*). When comparing results with the Bray-Curtis dissimilarity index, using data before disinfection as a reference, untreated skin zones showed similar index values five minutes and three hours after disinfection (p=0.0929). Although cream-treated zones were still dissimilar after three hours (p=0.089), they were also dissimilar to untreated zones at the same time point (p=0.026).

When assessing skin commensal and pathogen bacteria before and after disinfection, *Staphylococcus aureus* and *Staphylococcus hominis* were undetectable. Compared to before disinfection (*figure 1D*), the level of *Staphylococcus epidermidis* was unaffected by disinfection (p=0.230) and comparable between untreated and cream-treated areas three hours post-disinfection (p=0.801 and p=0.293, respectively). *Staphylococcus epidermidis* levels were also similar in both untreated and treated areas after three hours (p=0.193).

Ex vivo evaluation of wound healing by the repair complex

The healing efficacy of the repair complex from the wound repair cream was evaluated in a 3D human skin model by measuring evolution of the wound surface (n=1) (*figure 2A*). There were no differences between treatments at 4 and 14 days. However, compared to the negative control, a drastic reduction in wound surface was observed on day 7 with the repair complex (-82.0%) or EGF treatment (-92.4%).

Re-epithelialisation of the wound (*figure 2B-C*, n=1) in negative control model skin was gradual, leading to wound closure on day 14 with an immature epidermis lacking a stratum corneum. Upon topical treatment with EGF or the repair complex, wound edges already presented migrating epidermal tongues on day 4 that were obvious on day 7. On day 14, a contiguous, stratified, and terminally differentiated stratum corneum was observed.

Quantification of immunohistochemistry (*figure 3*, n=2) indicated that, compared to negative control model skin, both the EGF and the repair complex treatments increased the expression levels of epidermal markers (CD44, loricrin, Ki67), dermal-epidermal junction markers (collagen VII and XVII, except for the EGF treatment), and dermal markers (collagen III), analysed on day 4. In some cases, expression persisted to day 7, but was similar across treatments by day 14.

In vivo assessment of the short-terms effects of the wound repair cream

A number of short-term studies were carried out to assess the basic properties of the wound repair cream. The properties evaluated included skin adhesion, gas permeability, wound protection, and skin hydration.

Adherence of the cream to the skin was assessed by measuring variations in TEWL before applying the cream and 15 minutes later, just after attempting to remove it. A -20.9% TEWL decrease was observed (9.20 ± 0.58 g/h/m^2 before application *versus* 7.28 ± 0.46 g/h/m^2 15 minutes later, p<0.001), indicating that the cream reduces TEWL and that a significant amount remained on the skin.

Gas permeability measurements of O_2 and CO_2 (*table 2*) showed that while variations occurred in partial O_2 pressure between time points, no significant differences existed at any time point between the cream-treated and untreated forearm areas (p=0.993-1.000).

The cream's capacity to protect wounds from mechanical constraints was assessed by measuring TEWL after rubbing the skin with sandpaper. Results (*table 2*) indicated a significant increase in TEWL after abrasion in untreated skin zones, particularly after the first abrasion (+51%, p=0.048, after the first abrasion and 73%, p=0.001, after the second). Conversely, TEWL remained stable compared to baseline after a single cream application (p=0.984 after the first abrasion and p=1.000 after the second), resulting in significant differences compared to the untreated zone (-58%, p=0.006, for the first abrasion, and -55%, p<0.001 for the second).

The hydrating property of the cream was assessed by measuring skin hydration over eight hours (*table 2*). While no changes occurred in the untreated skin zone, a single application of the cream led to a significant 1.7-fold increase in skin hydration within one hour (p<0.001), with this increase persisting up to eight hours after application (+33%, p<0.001 compared to baseline).

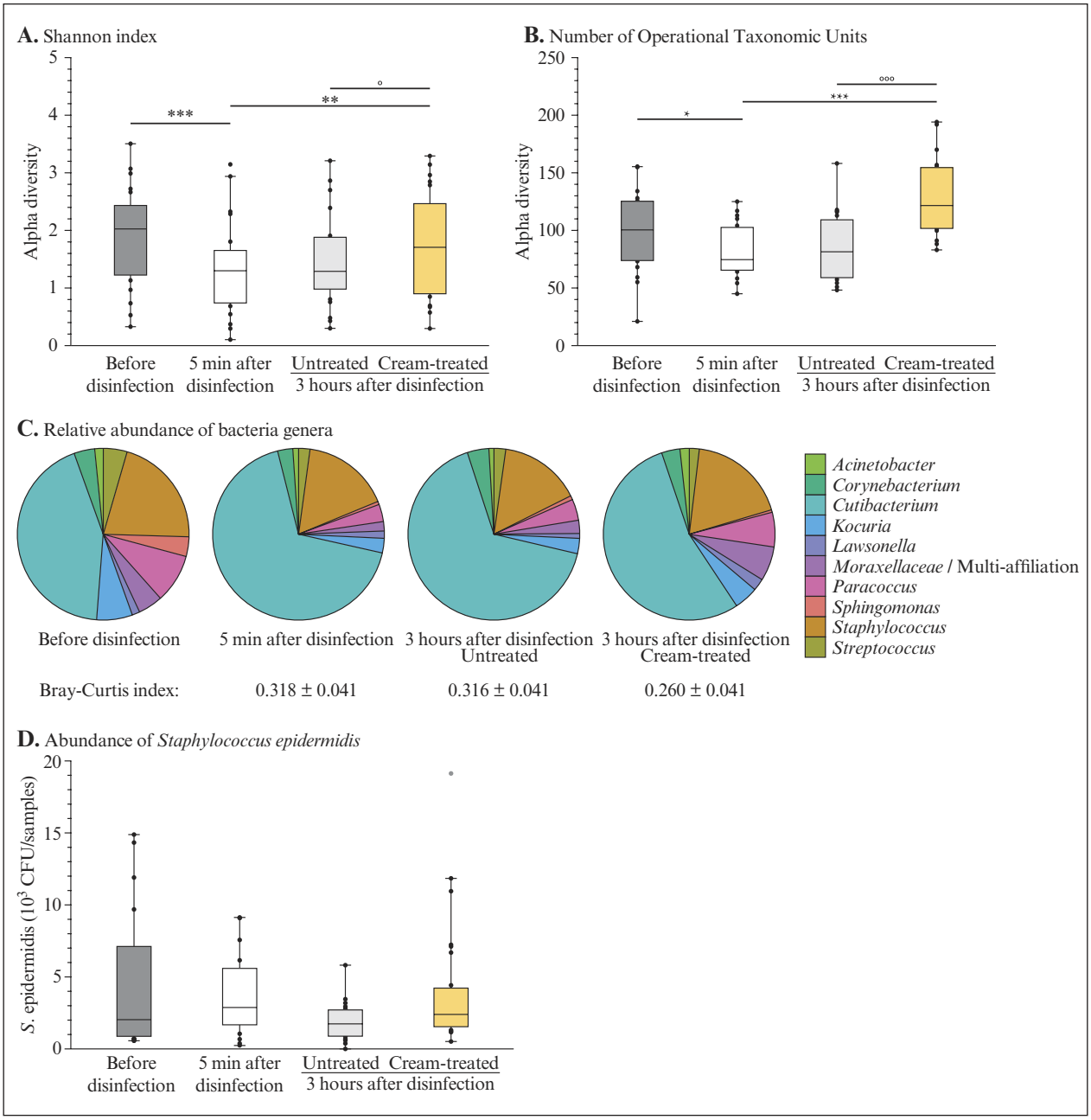

Figure 1. Restoration of skin microbiome diversity after disinfection and application, or not, of the wound repair cream. **A**) Shannon index. **B**) Number of operational taxonomic units. **C)** Relative abundance of the 10 most frequent bacterial genera of the skin microbiome based on Bray-Curtis index using data before disinfection as a reference. **D**) Level of *Staphylococcus epidermidis*. For panels (**A**), (**B**), and (**D**), only intra-treatment significance *versus* five minutes after disinfection is reported (*). Inter-treatment significant differences are only reported for identical time points (°). **p<0.05, ***p<0.01, °°°p<0.001.

Finally, the humectant properties of the cream were evaluated by monitoring the thickness of the stratum corneum and the living epidermis (*table 2*). Contrary to the untreated zone, the cream increased the thickness of the stratum corneum (p=0.018 after 30 minutes, p<0.001 after one hour). No variations were observed in the living epidermis.

Clinical evaluation of healing of erosive areas

The 14-day healing of erosive areas was analysed in order to compare wound repair cream-treated areas to those that received no treatment (*figure 4*).

Compared to untreated areas, TEWL decrease occurred earlier in cream-treated areas, with significant reductions

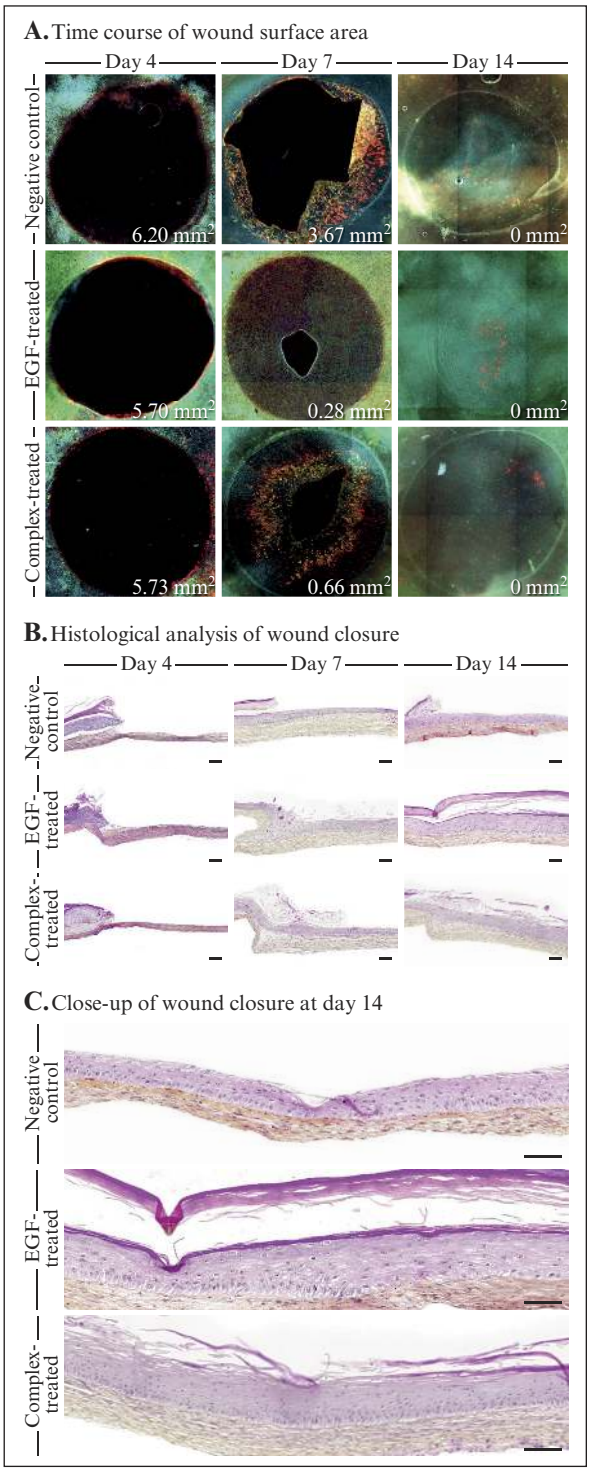

Figure 2. Time course of closure of a 3-mm diameter wound made in the epidermidis and dermis using a 3D human skin model upon topical application of mock treatment, EGF, or the repair complex. **A**) Wound surface area; the size of the wound surface area is presented in mm^2 in each panel. **B**, **C**) Histological analysis of wound closure. Scale bar: 100 µm.

observed as early as days 4 and 7 (-13%, p=0.016 and -28%, p=0.014, respectively). Besides, cream-treated areas displayed greater erythema on day 3 (+19.2%, p=0.037) but decreased erythema by day 7 (-21%, p=0.023). By day 7, reduced crust coverage, at the limit of significance, was also observed (-42%, p=0.071).
By day 4, subjects reported a faster reduction in functional signs (burning, tingling, and itching) in cream-treated areas compared to untreated areas (-55%, p=0.032). No adverse reactions or infections were reported.

Clinical evaluation of recovery after chemical peel

In a second clinical evaluation, we assessed the effects of the wound repair cream in a split-face comparative study of clinical and functional signs of subjects undergoing a chemical peel (*figure 5*).
Both cream- and placebo-treated hemifaces showed a reduction of inflammation, skin damage, and functional signs over time. However, compared to placebo-treated hemifaces, applications of the cream reduced inflammation by day 7 (-56%, p=0.037). Skin damage score was also reduced on day 7 (-45%, p=0.029) and day 3, at the limit of significance (-31%, p=0.069). Subjects reported no differences in pain and itching sensations between the cream- and the placebo-treated hemifaces. Moreover, the application of the cream after the peeling resulted in an almost immediate 43% reduction in heat sensation (p<0.01 compared to the placebo cream).
Combining all these clinical and functional results into a composite wound score, the wound repair cream led to significantly lower scores than the placebo on day 3 (-31%, p=0.032) and day 7 (-45%, p=0.017).
In both cream- and placebo-treated hemifaces, skin pH decreased one day after the chemical peel (-0.65 and -0.56 pH units, respectively; p<0.001) before returning to baseline on day 7 (pH=5.49 instead of 5.55 at baseline for both; p=0.162 for cream and p=0.245 for placebo). However, the decrease was less pronounced in cream-treated hemifaces on days 1 (pH=5.00 with the cream *versus* 4.90 with the placebo; p<0.001) and 3 (pH=5.14 with the cream *versus* 5.10 with the placebo; p=0.050).

Discussion

Results indicate that the wound repair cream promotes early restoration of microbiome diversity while not favouring pathogenic bacteria and preserving *Staphylococcus epidermidis*. The repair complex stimulates wound healing in a 3D human skin model. Short-term clinical studies revealed that the cream adheres to the skin and protects against mechanical stress while being permeable to gases and having hydrating properties. Upon clinical evaluation of healing of erosive areas, the wound repair cream was shown to reduce TEWL, wound severity, and functional signs. After a chemical peel, the cream limited pH variation.

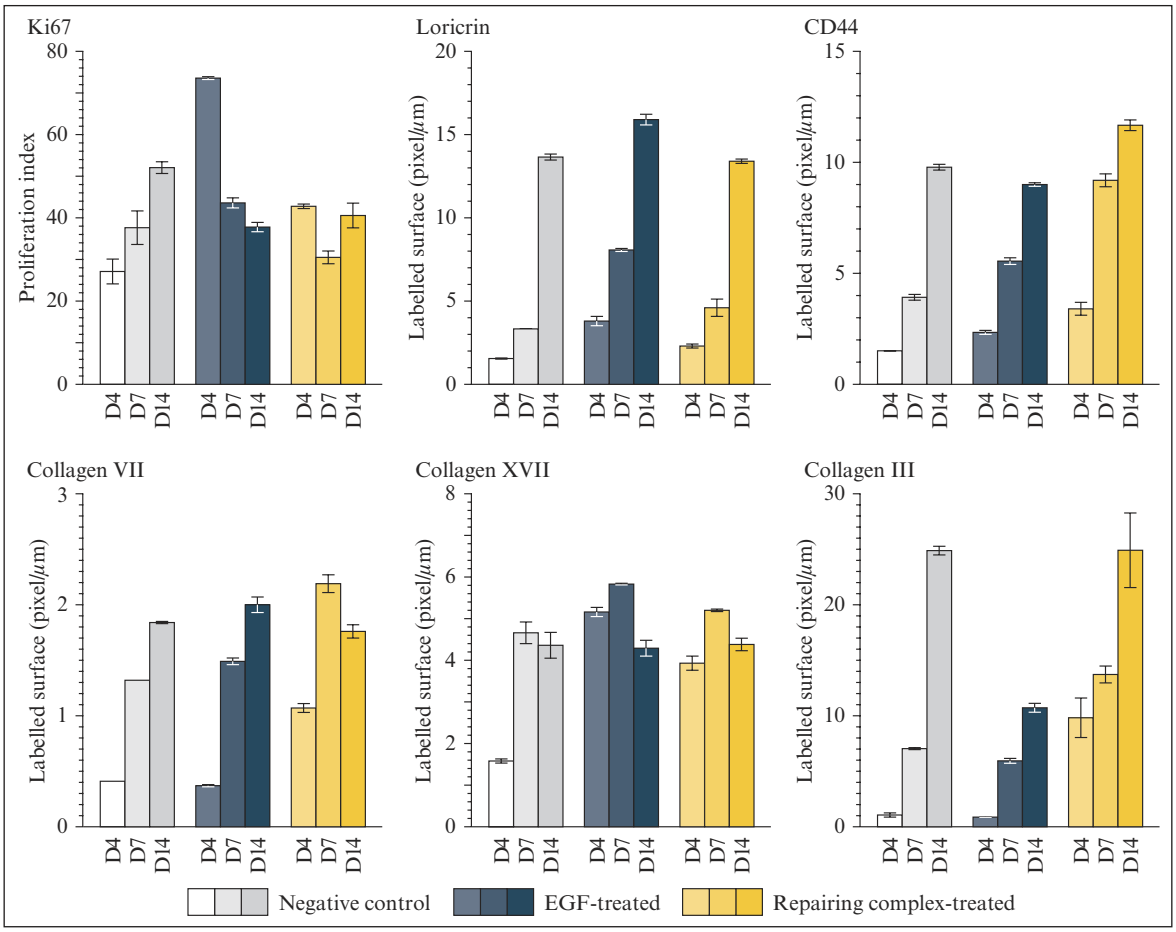

Figure 3. Immunohistochemical quantification of skin markers in the wounded area using the 3D wound-healing skin model upon topical application of mock treatment, EGF, or the repair complex. Ki67 quantification represents the proliferation index (*i.e.* the number of cells with labelled nuclei over the total number of cells), and the other markers are expressed as the surface area of pixels labelled within the wounded area normalised to dermal-epidermal junction length (for epidermal and dermal-epidermal markers) or the dermal area (for dermal markers). Results are expressed as mean ± standard deviation based on analysis of two independent model skin wound experiments for which two independent images were acquired per condition and per time point.

A distinctive feature of this study is that it is the first to assesses the effects of a wound repair cream on the skin microbiome. Indeed, the consensus has long been to disinfect wounds to prevent pathogen growth and infection, thereby killing most resident microorganisms. Yet, recent studies revealed that skin commensals play an important role in healing [12-14]. Therefore, the cream was formulated without ingredients that interfere with microorganisms. In particular, it contains no preservative or buffering ingredients likely to interfere with the microbiome or the skin. Therefore, it was of particular interest to evaluate the effect of the cream on the microbiome. The two diversity indexes highlight that the cream favours restoration of microbiome diversity. This is further supported by the Bray-Curtis index analysis of the 10 most frequent skin microbiome genera. Furthermore, the cream does not affect the level of *Staphylococcus epidermidis*. This is of crucial importance, given the role of most strains from this bacteria species in controlling pathogens, regulating wound healing, and reinforcing the skin barrier by participating in ceramide synthesis [15, 21]. Another essential role of a healthy microbiome is its crosstalk with the immune system, which supports the development and modulation of both innate and adaptive immunity, and contributes to the control of inflammation [22]. By strengthening the skin barrier, limiting chronic inflammation, and neutralising oxidative stress, commensal bacteria are not only critical to wound healing but may also play a protective role against skin cancer [23], underscoring the importance of preserving the beneficial skin microbiota when developing topical therapies.

The primary expectation for a wound repair cream is its capacity to promote wound closure. In a 3D skin model, the cream's repair complex performs similarly to EGF. It promotes the early expression of epidermal markers (CD44, loricrin, Ki67), indicating active cell division, barrier function restoration, and faster wound closure. It also stimulates the expression of dermal-epidermal junction markers (collagen VII and XVII), indicating its

Table 2. *In vivo* evaluation of the wound repair cream's short-term effects.

	Untreated zone	Treated zone
Gas permeability - O_2 partial pressure (mm Hg)		
T0	76.2 ± 2.1	75.1 ± 1.8
T30 min	68.9 ± 2.3	65.2 ± 2.5 *
T2h	69.3 ± 1.6	69.7 ± 1.8
T7h	65.6 ± 1.9 **	65.6 ± 1.8 *
Gas permeability - CO_2 partial pressure (mm Hg)		
T0	36.3 ± 0.7	36.1 ± 0.7
T30 min	37.1 ± 0.7	37.2 ± 0.6
T2h	37.0 ± 0.7	37.5 ± 0.7
T7h	38.1 ± 0.7	38.0 ± 0.7
Protection against abrasion - TEWL ($g/m^2/h$)		
Before cream application	7.3 ± 0.2	7.2 ± 0.2
15 minutes after 1st abrasion	11.1 ± 1.4 *	6.4 ± 0.3 °°
15 minutes after 2nd abrasion	12.6 ± 1.6 **	7.0 ± 0.3 °°°
Skin hydration - Corneometry analysis (A.U.)		
T0	25.8 ± 2.2	26.9 ± 1.7
T1 h	25.5 ± 2.3	44.5 ± 2.3 *** °°°
T3 h	25.9 ± 2.1	42.7 ± 2.2 *** °°°
T6 h	25.9 ± 2.2	37.1 ± 1.5 * °°
T8 h	26.1 ± 2.2	35.6 ± 1.4 °
Skin hydration - Variation in the thickness of the stratum corneum (µm)		
T0 *versus* 30 min after application	+0.5 ± 0.2	+1.5 ± 0.2 °
T0 *versus* 60 min after application	-0.5 ± 0.3 *	+1.3 ± 0.3 °°°
Skin hydration - Variation in the thickness of the living epidermis (µm)		
T0 *versus* 30 min after application	-0.7 ± 0.9	+0.9 ± 0.8
T0 *versus* 60 min after application	+0.3 ± 0.9	+0.2 ± 1.1

Results are expressed as mean ± standard error of the mean.
**Intra-treatment significance compared to T0 (for gas permeability and TEWL).*
°Inter-treatment significance for the same time point.
**p<0.5, ** or °°p<0.01 and ***or °°°p<0.001.*

role in reinforcement. Moreover, the repair complex strengthens the dermal extracellular matrix, as evidenced by increased expression of collagen III, a marker associated with the proliferative phase of wound healing [3]. The improved healing of erosive areas with the wound repair cream further supports these results. The reduced TEWL between days 4 and 7 indicates that the cream accelerates the restoration of a functional skin barrier and, thus, a mature stratum corneum. Furthermore, the reduced erythema observed on day 7 indicates decreased inflammation, suggesting an early transition to the next stage of wound healing: the proliferation stage [3]. These results parallel those observed in the 3D human skin model.

Several ingredients in the wound repair cream can explain these results. Moreover, experiments with the 3D wound-healing skin model indicate that the repair complex, composed of sodium hyaluronate, sodium polyglutamate, and xylose, is sufficient and effective in accelerating healing, even though not all ingredients were tested in this simplified model system. These compounds participate in the creation of a protective and moist environment [24-26]. In addition, hyaluronic acid also plays a pivotal role in immune cell recruitment, stimulating angiogenesis and promoting fibroblast and keratinocyte proliferation and migration [25-29]. The cream also contains ingredients that should contribute to its efficacy, especially biomimetic lipids, which aim to restore the skin barrier [30]. Deprived of anti-inflammatory ingredients, the cream includes an acetylated form of kyotorphin, which has analgesic properties [31, 32], potentially explaining the reduction in functional signs observed immediately after repair cream application following the chemical peel.

Besides assessing mechanically generated erosive areas, a peculiarity of this study was to evaluate the cream in a second model: a split-face analysis of the evolution of clinical and functional signs following a chemical peel. This study reveals that, similar to erosive areas, the wound repair cream effectively reduces clinical signs. Likely implying faster restoration of the mature stratum corneum, the application of the cream visibly reduces inflammation and skin damage. Additionally, the cream limits skin pH decrease after the procedure, with a maximum effect of 0.4 pH units after one day, and supports faster restoration of physiological skin pH. Indeed, the rationale behind the development of the cream was to preserve the skin ecosystem and avoid interfering with skin pH variations that are important for healing [33]. Furthermore, by favouring faster restoration of physiological pH, the cream should support the recovery of the microbiome, which is essential to maintaining skin homeostasis.

This study presents data spanning *in vitro* experiments to clinical evaluation, including split-face assessment. Conceived to restore and maintain the fragile skin equilibrium, according to the principles of ecobiology, results converge and consistently demonstrate that the wound repair cream stimulates the skin's repair mechanisms, provides a protective environment, and offers soothing properties. Containing no buffering ingredients, the cream does not interfere with pH variation, which is important for healing and early restoration of the skin's equilibrium. Deprived of preservatives, it fosters a healthy and diverse microbiome, preserving the essential *Staphylococcus epidermidis* species. Besides erosion wound healing and chemical peeling aftercare, the cream's multiple benefits should make it a useful addition to help improve the various skin lesions where hydration, soothing, and microbiome preservation are important, and it could be used for other minimally invasive dermo-cosmetic interventions, superficial burn injuries, surgical scars, *etc.* ■

Ethics statement: *the clinical assessment of the effect of the wound repair cream on erosive areas, conducted in Germany, was approved by the Institutional Review Board proDERM GmbH (23.0151-38 2023\|016). Performed in Poland, the post-peeling efficacy study was approved by the Bioethics Committee at the District Medical Chamber*

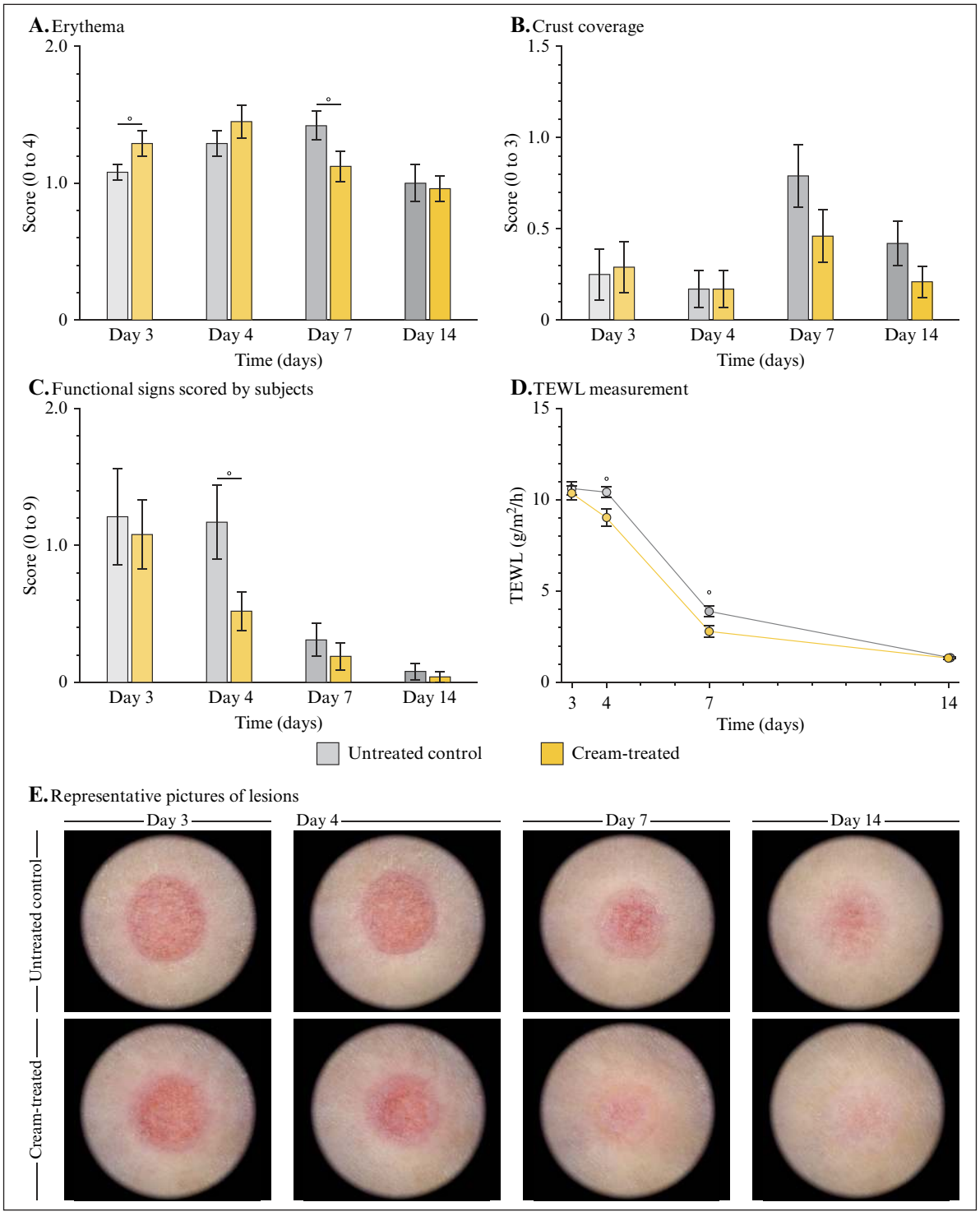

Figure 4. Time-course of the healing of erosive areas that received, or not, applications of the wound repair cream. **A**) Erythema rated by a dermatologist. **B**) Crust coverage scored by a dermatologist. **C**) Functional signs (burning, tingling and itching sensations) rated by subjects. **D**) TEWL measurement. **E**) Representative images of lesions. For panels (**A**), (**B**), (**C**) and (**D**), results are presented as mean ± SEM and only inter-treatment significance at the same time points is reported with °p<0.05.

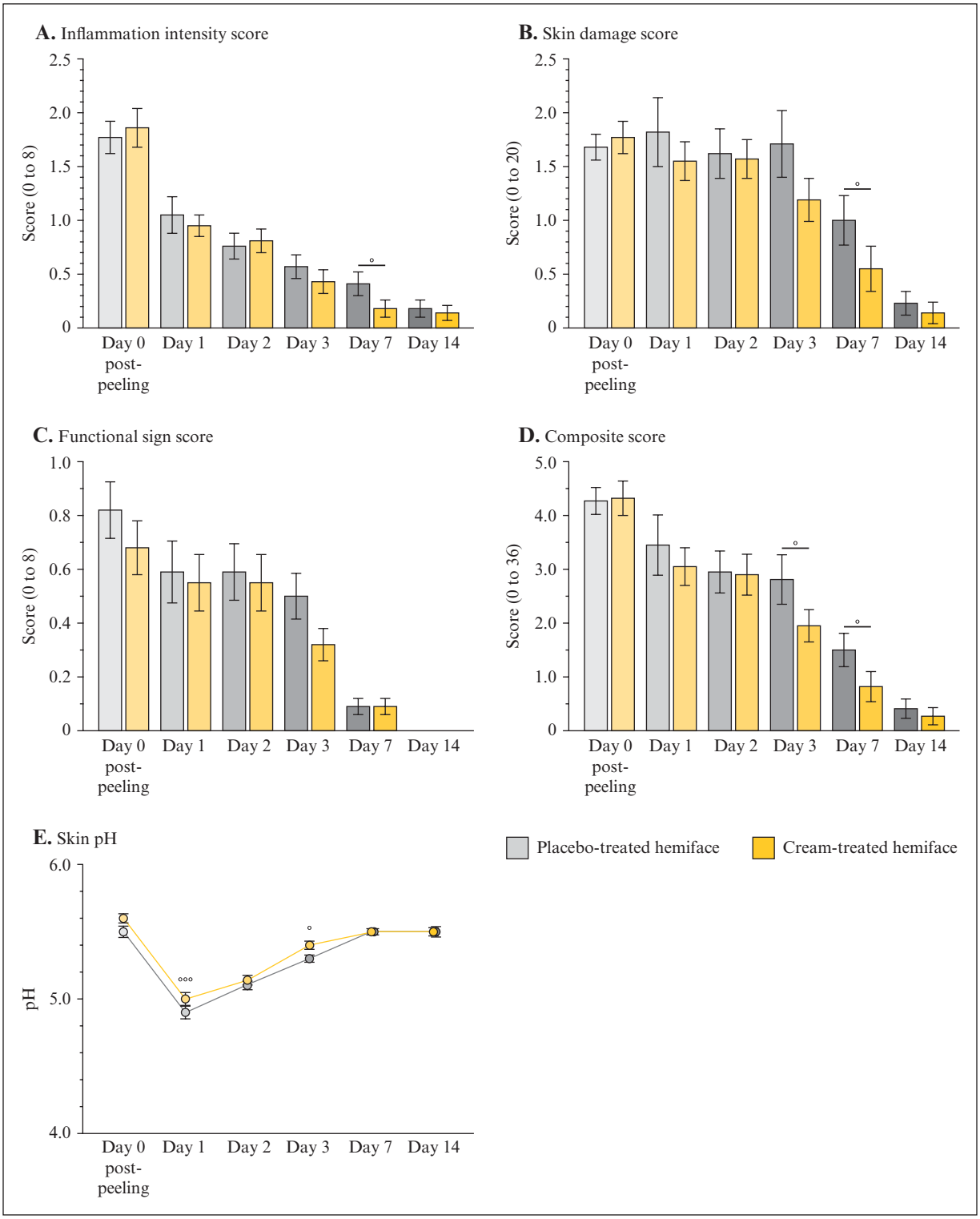

Figure 5. Time course of skin characteristics after a chemical peel. **A**) Clinical scoring of the intensity of inflammation. **B**) Clinical scoring of skin damage. **C**) Subject-reported functional signs. **D**) Composite score. **E**) Instrumental measurement of skin pH. Results are presented as mean ± SEM and only inter-treatment significance at the same time points is reported with °p<0.05 and °°°p<0.001.

in Gdansk (KB – 955 / 2022 / 12.07.2022). The other studies, being non-invasive studies of a cosmetic product, required no approval by ethics committees according to local (France) and EU regulations. All studies complied with the Declaration of Helsinki and all subjects gave their written informed consent.

Data availability: the data generated and analysed are available from the corresponding author upon reasonable request.

Funding: this work has been entirely funded by NAOS.

Conflicts of interest: HP, SC, MaS, EA, AB, BC, FG, JS, NR, NA, MiS, ST, EPM, and CG are or were full-time employees of NAOS. BD received counselling honorarium from NAOS.

Acknowledgements: the authors thank Anastasia Launay (NAOS Ecobiology Company) for the bibliographic research and selection of the active ingredients of the repair complex, Dr Marlène Chavagnac-Bonneville (NAOS Ecobiology Company) for her support with the manuscript, and Dr. Burty-Valin (NAOS Ecobiology Company) for her critical reading of the manuscript. The authors also wish to thank Dr Philippe Crouzet, Estium-Concept, for scientific writing services.

References

1. Alves PJ, Barreto RT, Barrois BM, Gryson LG, Meaume S, Monstrey SJ. Update on the role of antiseptics in the management of chronic wounds with critical colonisation and/or biofilm. *Int Wound J* 2021; 18: 342-58.

2. Cañedo-Dorantes L, Cañedo-Ayala M. Skin Acute Wound Healing: A Comprehensive Review. *Int J Inflam* 2019; 2019: 3706315.

3. Fernández-Guarino M, Hernández-Bule ML, Bacci S. Cellular and Molecular Processes in Wound Healing. *Biomedicines* 2023; 11: 2526.

4. Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci Transl Med* 2014; 6: 265sr6.

5. Agren MS, Karlsmark T, Hansen JB, Rygaard J. Occlusion versus air exposure on full-thickness biopsy wounds. *J Wound Care* 2001; 10: 301-4.

6. Korting HC, Schöllmann C, White RJ. Management of minor acute cutaneous wounds: importance of wound healing in a moist environment. *J Eur Acad Dermatol Venereol* 2011; 25: 130-7.

7. Wigger-Alberti W, Kuhlmann M, Ekanayake S, Wilhelm D. Using a novel wound model to investigate the healing properties of products for superficial wounds. *J Wound Care* 2009; 18: 123-31.

8. Wigger-Alberti W, Stauss-Grabo M, Grigo K, Atiye S, Williams R, Korting HC. Efficacy of a tyrothricin-containing wound gel in an abrasive wound model for superficial wounds. *Skin Pharmacol Physiol* 2013; 26: 52-6.

9. Eberlein T, Gerke P, Lorenz H, Ammer R. Advantages in wound healing by a topical easy to use wound healing lipo-gel for abrasive wounds - Evidence from a randomized, controlled experimental clinical study. *Wound Med* 2016; 15: 11-19.

10. Kuhlmann M, Wigger-Alberti W, Mackensen YV, *et al.* Wound healing characteristics of a novel wound healing ointment in an abrasive wound model: A randomised, intra-individual clinical investigation. *Wound Med* 2019; 24: 24-32.

11. Brocario A, Maurel S, Kapoor K, Lauze C, Favrel S. Assessment of wound healing efficacy and tolerability using Cicatryl™ cream based on a suction blister model in healthy subjects. *Eur J Dermatol* 2023; 32: 762-69.

12. Canchy L, Kerob D, Demessant A, Amici JM. Wound healing and microbiome, an unexpected relationship. *J Eur Acad Dermatol Venereol* 2023; 37: 7-15.

13. Tomic-Canic M, Burgess JL, O'Neill KE, Strbo N, Pastar I. Skin Microbiota and its Interplay with Wound Healing. *Am J Clin Dermatol* 2020; 21: 36-43.

14. White EK, Grice EA. The Wound Microbiome. *Cold Spring Harb Perspect Biol* 2023; 15: a041218.

15. Zheng Y, Hunt RL, Villaruz AE, *et al.* Commensal *Staphylococcus epidermidis* contributes to skin barrier homeostasis by generating protective ceramides. *Cell Host Microbe* 2022; 30: 301-13.

16. Sams-Dodd J, Sams-Dodd F. Time to Abandon Antimicrobial Approaches in Wound Healing: A Paradigm Shift. *Wounds* 2018;30(11):345-52.

17. Dréno B. The microbiome, a new target for ecobiology in dermatology. *Eur J Dermatol* 2019; 29: 15-8.

18. Radman M. Ecobiological approach to research regarding ageing and diseases. *Eur J Dermatol* 2019; 29: 11-4.

19. Lluch J, Servant F, Païssé S, *et al.* The Characterization of Novel Tissue Microbiota Using an Optimized 16S Metagenomic Sequencing Pipeline. *PLoS One* 2015; 10: e0142334.

20. Shin SH, Koh YG, Lee WG, Seok J, Park KY. The use of epidermal growth factor in dermatological practice. *Int Wound J* 2023; 20: 2414-23.

21. Brown MM, Horswill AR. *Staphylococcus epidermidis*-Skin friend or foe? *PLoS Pathog* 2020; 16: e1009026.

22. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res* 2020; 30: 492-506.

23. L'Orphelin JM, Dompmartin A, Dréno B. The Skin Microbiome: A New Key Player in Melanoma, From Onset to Metastatic Stage. *Pigment Cell Melanoma Res* 2025; 38: e13224.

24. Bravo B, Correia P, Gonçalves Junior JE, Sant'Anna B, Kerob D. Benefits of topical hyaluronic acid for skin quality and signs of skin aging: From literature review to clinical evidence. *Dermatol Ther* 2022; 35: e15903.

25. Choi JC, Uyama H, Lee CH, Sung MH. Promotion Effects of Ultra-High Molecular Weight Poly-γ-Glutamic Acid on Wound Healing. *J Microbiol Biotechnol* 2015; 25: 941-5.

26. Serra M, Gudina E, Botelho C, Teixeira JA, Barros AN. Polyglutamate: Unleashing the Versatility of a Biopolymer for Cosmetic Industry Applications. *Cosmetics* 2024; 11: 76.

27. Karvinen S, Pasonen-Seppänen S, Hyttinen JM, *et al.* Keratinocyte growth factor stimulates migration and hyaluronan synthesis in the epidermis by activation of keratinocyte hyaluronan synthases 2 and 3. *J Biol Chem* 2003; 278: 49495-504.

28. Genasetti A, Vigetti D, Viola M, *et al.* Hyaluronan and human endothelial cell behavior. *Connect Tissue Res* 2008; 49: 120-3.

29. Frenkel JS. The role of hyaluronan in wound healing. *Int Wound J* 2014; 11: 159-63.

30. Chandan N, Rajkumar JR, Shi VY, Lio PA. A new era of moisturizers. *J Cosmet Dermatol* 2021; 20: 2425-30.

31. Takagi H, Shiomi H, Ueda H, Amano H. Morphine-like analgesia by a new dipeptide, L-tyrosyl-L-arginine (Kyotorphin) and its analogue. *Eur J Pharmacol* 1979; 55: 109-11.

32. Resende DISP, Ferreira MS, Sousa-Lobo JM, Sousa E, Almeida IF. Usage of Synthetic Peptides in Cosmetics for Sensitive Skin. *Pharmaceuticals* (Basel) 2021; 14: 702.

33. Sim P, Strudwick XL, Song Y, Cowin AJ, Garg S. Influence of Acidic pH on Wound Healing *In Vivo*: A Novel Perspective for Wound Treatment. *Int J Mol Sci* 2022; 23: 13655.