Article

Performance and Tolerability of a New Topical Dexpanthenol-Containing Emollient Line in Subjects with Dry Skin: Results from Three Randomized Studies

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Abstract: Three studies were conducted with three new dexpanthenol-containing emollients containing increasing lipid contents (Emollients 1–3) to assess their performances in healthy adults with dry skin. All three studies (N = 42 each) followed virtually the same design. A single skin application of the study product was performed followed by once-daily usage. Skin hydration, transepidermal water loss (TEWL), skin biomechanical properties, and lipid content of the stratum corneum (SC) were regularly assessed over the 28-day study period; a subset (N = 22) underwent a sodium lauryl sulfate (SLS) challenge prior to product application. All three emollients were well tolerated and showed good performances with only minor differences in instrumental measurements. After single and prolonged once-daily applications of Emollients 1–3 to dry skin and dry SLS-damaged skin, skin hydration significantly increased from baseline (BL) (by 38.1–72.4% in unchallenged skin, $p < 0.001$ for all three). This was paralleled by significant increases in skin elasticity parameters. Usage of Emollients 1 and 3 caused increases from BL in SC cholesterol (by 9.8–12.5%, $p < 0.05$ for both) and SC free fatty acid levels (by 3.7–26.3%, $p < 0.05$ for both) at the end of the study. No sustained effects on TEWL were recorded. Our findings support the once-daily use of all three emollients in adults with dry skin.

Keywords: dexpanthenol; dry skin; emollient; topical

1. Introduction

Dry skin (xerosis) is associated with various skin conditions (e.g., atopic dermatitis, irritant contact dermatitis, or psoriasis); however, it can also be a condition itself [1]. Frequently, it is accompanied by itch and impaired quality of life. A recent study conducted in Germany showed that almost 30% of the general population >16 years suffer from dry skin, with an increasing prevalence with age [2]. Hence, dry skin represents a highly prevalent and burdensome condition. Typically, the condition is characterized by rough or flaky skin showing reduced elasticity and mechanical features [3]. The stratum corneum (SC) of dry skin reveals an altered lipid organization/composition as well as lipid content which strongly contributes to the development of an impaired skin barrier function with increased transepidermal water loss (TEWL) and eventually xerosis [1]. The onset of dry skin may be triggered by genetic disposition, environmental factors, ageing, or other factors (e.g., internal diseases or drugs) [1,2,4].

Topical application of emollients represents an important part of dry skin management. Key constituents of an ideal emollient have been defined based on latest research findings, and there was a call to use the gained insights for the development of new formulations [1]. Specifically, an ideal emollient should include the following five key components: non-

physiological lipids, physiological lipids, humectants, antipruritics/soothing agents, and agents supporting epidermal differentiation [1,5].

Against this background, three new topical dexpanthenol-containing emollients (Emollients 1–3) were developed for subjects with dry skin conditions. All three emollients are oil-in-water emulsion formulations to be used as cosmetic products for daily care. Key ingredients are the same in the three preparations and comprise dexpanthenol, argan oil, shea butter, squalane, glycerin, niacinamide, and isopropyl isostearate, a composition also called the "repair complex". The preparations differ in lipid content (i.e., shea butter, squalane, and isopropyl isostearate), with Emollient 1 (Bepanthen® Derma RESTORING Daily Body Lotion) containing the lowest amount of lipids and Emollient 3 (Bepanthen® Derma INTENSE REPAIRING Daily Body Balm) the highest. Emollient 2 (Bepanthen® Derma REPLENISHING Daily Body Lotion) has an intermediate lipid content. Thus, the three emollients address individual needs of dry skin sufferers. The compositions of Emollients 1–3 comply with those of an ideal emollient [1]. Glycerin acts as humectant [6], niacinamide (nicotinamide) as an antipruritic/soothing agent [7,8], and dexpanthenol as a multifunctional ingredient—its functions include the enhancement of epidermal differentiation [1,9]. In addition, Emollients 1–3 contain nonphysiological lipids (argan oil, shea butter, squalane) and physiological lipids (isopropyl isostearate) which act as substitutes for lost natural skin lipids in the outer layers of the SC and contribute to normalization of the altered lipid organization/composition in the SC, respectively [1,10–12].

The performance and cutaneous tolerability of each of the new emollients were explored in a randomized study involving healthy adult subjects with dry skin. Effects on SC hydration, TEWL, skin biomechanical properties, and SC lipid content were assessed before, during, and at the end of the 28-day study period. All three studies followed a similar design.

2. Methods

The three studies were conducted in healthy adult subjects under supervision of a dermatologist at Eurofins Evic Product Testing Romania SRL, Bucharest, Romania, between September 2019 and February 2020. The trials were performed according to the general requirements of the Declaration of Helsinki with all its amendments. Subjects gave written informed consent to participate after being informed about study procedures. The new emollients applied in the trials were provided by Bayer Consumer Care AG, Basel, Switzerland. For all three studies, ethics approval was obtained from an independent Institutional Ethics Committee.

Given the exploratory nature of the three studies, no formal sample size calculation was carried out. For the same reason, no primary and secondary variables were defined. Based on previous studies, it was expected that meaningful results can be gained with the selected sample size [13,14].

2.1. Study 1: Emollient 1—Containing the Lowest Amount of Lipids

2.1.1. Study Design

Study 1 was an open-label, randomized, intraindividual comparison study in healthy adult subjects with dry and sensitive skin. Study visits took place on day 0 (baseline) and study days 1, 2, 7, 14, 21, and 28. In a subset of subjects (called "subgroup"), skin barrier dysfunction was experimentally induced at one skin area on each volar forearm by application of 0.8% sodium lauryl sulfate (SLS, 1 mL) under a semiocclusive patch (Tegaderm®, 3M Health Care, Neuss, Germany) for 24 h. Subjects undergoing SLS challenge had an additional study visit on day -1 to have SLS and patch applied.

There was no overnight confinement of study participants, and subjects returned to the study site without having applied Emollient 1 on that day.

All subjects had the test areas A0, A1, A2 marked on their volar forearms. A0 and A1 were always on the same arm while A2 was located on the contralateral arm. The subgroup had two additional marked areas on the volar forearms (A3 and A4) for the SLS

challenge. A3 and A4 were to be placed on different forearms. Every test area had a size of 16 cm^2, except A0 which had a size of 5 cm^2. Emollient 1 was always applied on the same skin areas of one volar forearm (A0, A1, A3). The areas of the contralateral arm (A2, A4) served as controls and remained untreated with Emollient 1. The locations of A0, A1, and A3 on the same forearm were chosen by randomization. Likewise, the allocation of forearms (left or right) to Emollient 1 treatment was carried out according to a balanced randomization scheme.

Approximately 2 mg/cm^2 of Emollient 1 was to be applied on the assigned skin areas on a once-daily schedule. The first application was made with the help of a technician at the study site on day 0 following baseline assessments. No study product was applied on days 1 and 2. Thereafter, the application of Emollient 1 was performed by the subjects themselves at home until day 28. In subjects of the subgroup, SLS patches were removed 30 min before first application (day 0, baseline). At that time, the SLS challenge had been completed. Compliance was verified by weighing each container with Emollient 1 (200 mL plastic tubes) before and after the application period.

2.1.2. Subjects and Assessments

Healthy male and female subjects between 18 and 70 years of age and having skin types II–IV on the Fitzpatrick scale [15] were eligible for study participation. Subjects were required to have very dry, flaky, and sensitive skin as judged clinically by the study's dermatologist. For inclusion, females had to be nonpregnant and nonbreastfeeding. Female subjects of childbearing age were required to use reliable methods of contraception during the study.

Subjects were excluded if they had: any skin condition at the target area that would interfere with interpretation of study results (e.g., atopic skin, excessive pilosity, scars, irritated skin, pigmentation disorders); a condition requiring the use of drugs interfering with study assessments within 6 months (systemic retinoids), 3 months (other systemic antiacne medication), 2 months (topical retinoids), 1 month (other topical antiacne medication), or within 2 weeks (antibiotics, antiacne cosmetic products, topical or systemic use of anti-inflammatory drugs or antihistamines) before or during the study; started/changed estrogen-progesterone contraception or hormonal treatment within 3 months before or during the trial; allergies to any ingredient of the study product; history of adverse reactions to cosmetic products; vaccination within 2 weeks prior to or during the trial; or desensitization treatment within 6 months before start of the study.

Subjects were not allowed to have had any noninvasive (e.g., scrub, cleansing) or invasive (e.g., laser treatment, peeling) cosmetic interventions on the test areas within 1 month and 2 months, respectively, prior to and during the study. Similarly, intensive exposure of test areas to ultraviolet light was not permitted within 1 month before and throughout the trial. Subjects were also not allowed to use topical preparations other than the study product on the target area during the course of the study. On days of study visits, subjects had to come to the trial center without having applied anything on the forearms. Moreover, the use of detergents was not allowed on test areas since the previous evening; neither was the consumption of hot beverages within 2 h before instrumental measurements.

SC hydration was assessed by corneometry (Corneometer$^{\circledR}$ CM825, Courage & Khazaka, Cologne, Germany), which determines the electrical capacitance of the skin surface. Capacitance is considered a function of the SC water content [16]. Measurements were conducted on each of the two test areas (A1 and A2) at baseline and at 1, 2, 5, 24 (day 1), and 48 h (day 2) after the first and single application of Emollient 1. Additional measurements took place on study days 7, 14, 21, and 28. In subjects of the subgroup, SC hydration was also quantified in skin areas A3 and A4. For these areas, the assessment time schedule was the same as for areas A1 and A2, except for an additional measurement on day -1 before SLS application and omission of the day-21 and day-28 assessments. Three measurements

were performed in the skin areas per assessment time. An increase in corneometry/skin capacitance values reflects improved skin hydration [17].

TEWL (MPA Tewameter® TM300, Courage & Khazaka, Cologne, Germany) measurements were performed on the allocated skin areas (A1 and A2) according to the same time schedule as SC hydration assessments. In subjects of the subgroup, no TEWL measurement took place on days 21 and 28, but TEWL was additionally quantified in skin areas A3 and A4 on day -1 of SLS application. There was one measurement per test area and assessment time. TEWL represents a sensitive and noninvasive method to quantify SC barrier function; a decrease in TEWL corresponds to an improvement in this function [18,19].

The Cutometer® MPA580 (Courage & Khazaka, Cologne, Germany) was used to evaluate biomechanical properties of the skin. It is a noninvasive, objective suction method to evaluate the effect of dermatological and cosmetic products on skin mechanics [20]. Details on the methodology and measured parameters have been reported previously [20–23]. In brief, the Cutometer® creates a negative pressure by suction which draws the skin into the aperture of the probe (i.e., upper layers of the skin are stretched vertically). The resistance of the skin to being sucked up (firmness) and its ability to return to its initial position (elasticity) are graphically shown [24]. In our study, total skin distensibility (Uf), immediate distensibility (Ue), and immediate recovery (Ur) were derived from the deformation by time curve [22]. The relative parameters Ur/Ue (net elasticity) and Ur/Uf (ratio of elastic recovery to distensibility) were calculated. Data were generated using the device software. Both Ur/Ue and Ur/Uf are elasticity parameters which decrease with aging [22,23]. The proportion of subjects for whom there was an improvement of skin firmness, skin suppleness, and skin elasticity— as defined in Figure 1—were calculated and entitled "positive subjects". Biomechanical skin measurements were conducted on each of the two test areas (A1 and A2) at baseline and on days 7, 14, 21, and 28. One measurement was performed in the allocated skin areas per assessment time.

Effect on	Parameters			
	Ue	Uf	Ur/Ue	Ur/Uf
Skin firmness	↓	↓	↑ or =	↑ or =
Skin suppleness	↑	↑	↑ or =	↑ or =
Skin elasticity	↑	↑		
	→	→	↑	↑
	↓	↓		

Figure 1. Definitions of skin firmness, skin suppleness and skin elasticity applied in the study. Ue = immediate distensibility, Uf = total skin distensibility, Ur = immediate recovery, Ur/Ue = net elasticity, Ur/Uf = ratio of elastic recovery to distensibility.

Skin surface samples (swab samplings) for quantification of SC lipids involved in barrier function (i.e., ceramides, cholesterol, and free fatty acids) were taken at baseline and on days 7 and 28. Two swab samplings were collected per assessment time by rubbing them on the skin of area A0. The swabs were previously soaked in an aqueous nonionic surfactant solution (Synelvia, Labège, France—proprietary method). Subsequently, the swab heads were placed in Eppendorf tubes and frozen at −20 °C until analysis by liquid or gas chromatography both coupled with a mass spectrometer [25].

Before instrumental measurements (corneometry, TEWL, skin biochemical parameters), subjects remained in a climatized room (20 ± 2 °C, 45 ± 15% relative humidity) for 15–20 min. The skin areas treated with Emollient 1 were to be wiped with a paper towel before measurements to remove the excess product. If different instrumental measurements

were performed in the same skin area at a given time-point, different skin sites have been used. Monitoring of adverse events (AEs) took place over the entire study period.

2.1.3. Statistical Evaluation

All statistical analyses were performed using SPSS (version 22, IBM, Armonk, NY, USA). For corneometry and TEWL measurements, a global repeated measures analysis of variance (ANOVA) was conducted to test if there was any difference between the mean values determined at baseline and subsequent measurements. The paired *t*-test or Wilcoxon signed-rank test (depending on data distribution) was used to identify any significant mean change in instrumental or lipid content measurements between baseline and each postbaseline assessment. Differences in corneometry and TEWL values between Emollient 1-treated and nontreated areas were statistically analyzed using a paired *t*-test. Generally, the level of significance was set at 0.05. For analysis of data from instrumental measurements (change from baseline), a Bonferroni correction was applied to deal with multiple testing for comparisons over time. In these cases, the p-level for significance was lower. AEs were evaluated descriptively.

2.2. Study 2: Emollient 2—Containing an Intermediate Amount of Lipids

The design, inclusion/exclusion criteria, and assessments of Study 2 were identical to Study 1, with the exception that subjects were not required to have sensitive skin as judged clinically by the study's dermatologist.

2.3. Study 3: Emollient 3—Containing the Highest Amount of Lipids

The design, inclusion/exclusion criteria, and assessments of Study 3 were identical to Study 1, with the exception that subjects were not required to have sensitive skin as judged clinically by the study's dermatologist.

3. Results

3.1. Study 1: Emollient 1—Containing the Lowest Amount of Lipids

In total, 42 healthy Caucasian subjects (all females) were enrolled and all completed the study. The mean age was 59 years (range: 35–70 years). The subgroup undergoing SLS challenge consisted of 22 subjects.

3.1.1. SC Hydration (Corneometry)

At baseline, the two skin areas treated with Emollient 1 (A1) or left untreated (A2) had comparable mean $\pm$ standard deviation (SD) values for dryness (24.51 ± 4.68 and 25.13 ± 5.09 arbitrary units (a.u.), respectively). Table 1 displays the corneometry results for the Emollient 1-treated area over the course of the study; mean absolute values, and mean changes from baseline of skin surface capacitance are shown. The single application of Emollient 1 as well as the subsequent once-daily treatment triggered an increase in SC hydration as mirrored by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.001$ for all comparisons with baseline). In addition, global ANOVA revealed a significant difference between the skin capacitance mean value determined at baseline and subsequent measurements ($p < 0.05$). After single application, the skin-hydrating effect was most pronounced at the early measurements but was still apparent after 48 h. On day 28, there was a 63.9% improvement in skin hydration compared to baseline (+14.07 a.u.; $p < 0.001$). In the untreated control area (A2), no increase in SC hydration from baseline was observed. In fact, mean electrical capacitance remained unchanged at 25–26 a.u. throughout the study. Bilateral differences between Emollient 1-treated and untreated areas, in terms of absolute mean values for skin capacitance, were significant and in favor of Emollient 1 at all postbaseline assessments (Figure 2). On day 28, the mean bilateral difference amounted to 13.53 a.u. ($p < 0.001$).

Table 1. Absolute skin capacitance measurement values and changes from baseline after single application of Emollient 1 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	24.51 ± 4.68	-	-
1 h	42.85 ± 13.19	18.34 ± 13.92	<0.001 [#]
2 h	41.48 ± 14.28	16.98 ± 14.55	<0.001 [#]
5 h	37.41 ± 10.66	12.90 ± 10.18	<0.001 [#]
24 h	31.90 ± 7.50	7.39 ± 7.75	<0.001 [#]
48 h	31.23 ± 6.68	6.72 ± 7.43	<0.001 [#]
Day 7	37.89 ± 11.09	13.38 ± 12.13	<0.001 [§]
Day 14	38.55 ± 7.61	14.04 ± 7.78	<0.001 [§]
Day 21	42.21 ± 7.85	17.71 ± 7.50	<0.001 [§]
Day 28	38.58 ± 6.68	14.07 ± 7.97	<0.001 [§]

N = 42. Data are given in arbitrary units (a.u.). The values were assessed by corneometry in area A1 (= treated with Emollient 1) and are presented as mean ± SD. BL = Baseline skin capacitance value before first product application; h = hour. * For mean change from baseline, paired *t*-test. [#] Significant if $p < 0.01$ (Bonferroni correction). [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: An increase in skin capacitance reflects a skin-hydrating effect.
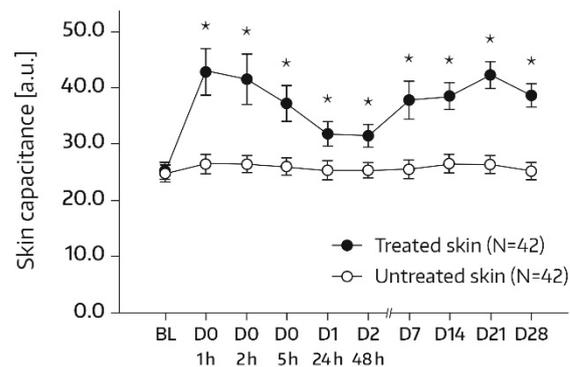

Figure 2. Results from skin capacitance measurements in untreated skin and skin undergoing a single application of Emollient 1 (first 48 h) followed by once-daily application for 26 days. The values were assessed by corneometry and are presented as mean ± SD. BL = Baseline skin capacitance value before first product application; D = day; h = hour. * $p < 0.001$ if compared to untreated control, paired *t*-test.

Similarly, in subjects of the subgroup, skin hydration increased significantly in skin that had undergone SLS-induced damage and was subsequently treated with Emollient 1. On day 14, there was a 113.8% improvement in skin hydration compared with baseline (+17.93 a.u.; $p < 0.001$). Bilateral differences between Emollient 1-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4), in terms of absolute values for skin capacitance, were significant and in favor of Emollient 1 at most postbaseline assessments (Figure 3). On day 14, the mean bilateral difference amounted to 13.85 a.u. ($p < 0.001$). The increase in skin hydration in the untreated skin area (A4) during the first 48 h following SLS patch removal can be attributed to transient inflammatory reactions, as reported previously [13].
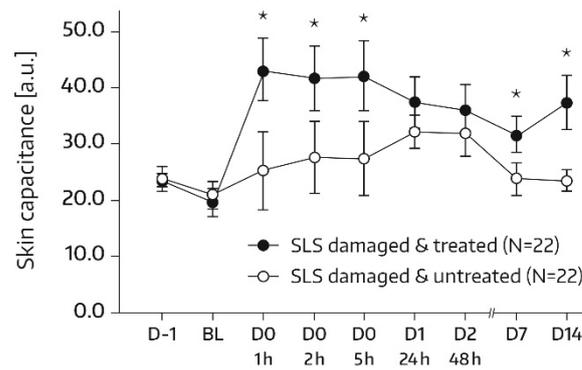
Figure 3. Results from skin capacitance measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 1 (first 48 h) followed by once-daily application for 12 days. The values were assessed by corneometry and are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment). BL = Baseline skin capacitance value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate.* $p < 0.001$ if compared to untreated control, paired *t*-test.

3.1.2. Transepidermal Water Loss

Mean TEWL baseline values were comparable between Emollient 1-treated (A1) and nontreated (A2) skin areas (11.00 ± 3.09 and 10.54 ± 2.42 g/m^2/h, respectively). Table 2 shows TEWL results assessed in the Emollient 1-treated area over the study; mean absolute values and mean changes from baseline for TEWL values are displayed. Mean TEWL decreased significantly at 1 h following first application of Emollient 1. However, the effect was not consistent over the study period. On day 28, there was an 11.0% decrease in TEWL compared with baseline (-1.87 g/m^2/h; $p = 0.003$), indicating improved skin barrier function at the end of the study. In the untreated control area (A2), TEWL values remained essentially unchanged throughout the study showing mean TEWL changes from baseline between -0.72 and 0.12 g/m^2/h ($p > 0.05$ for all comparisons with baseline). Bilateral differences between Emollient 1-treated and untreated areas, in terms of absolute mean values for TEWL, were not significant at all postbaseline assessments (data not shown).

Table 2. Absolute transepidermal water loss (TEWL) measurement values and changes from baseline after single application of Emollient 1 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	11.00 ± 3.09	-	-
1 h	9.62 ± 1.84	-1.38 ± 2.75	0.002 [#]
2 h	9.54 ± 2.95	-1.46 ± 4.47	0.040 [#]
5 h	9.87 ± 2.73	-1.13 ± 3.73	0.057 [#]
24 h	11.12 ± 3.93	0.12 ± 5.24	0.884 [#]
48 h	10.68 ± 3.90	-0.32 ± 4.15	0.617 [#]
Day 7	11.32 ± 4.82	0.32 ± 5.18	0.693 [§]
Day 14	9.94 ± 2.19	-1.06 ± 3.27	0.042 [§]
Day 21	9.43 ± 2.53	-1.57 ± 3.99	0.015 [§]
Day 28	9.13 ± 2.00	-1.87 ± 3.82	0.003 [§]

N = 42. Data are given in g/m^2/h. The values were assessed in area A1 (= treated with Emollient 1) and are presented as mean ± SD. BL = Baseline TEWL value before first product application; h = hour. * For mean change from baseline, paired *t*-test. [#] Significant if $p < 0.01$ (Bonferroni correction). [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: A reduction in TEWL reflects improvement in skin barrier function.

In subjects of the subgroup, the SLS challenge caused skin barrier dysfunction as reflected by an approximately 2-fold increase in TEWL at baseline compared with unchallenged test areas at day -1. By day 14, mean TEWL had reached the prechallenge niveau, indicating restoration of skin barrier function. However, this applied to both treated and untreated skin. In fact, bilateral differences between Emollient 1-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4) were not apparent (Figure 4).
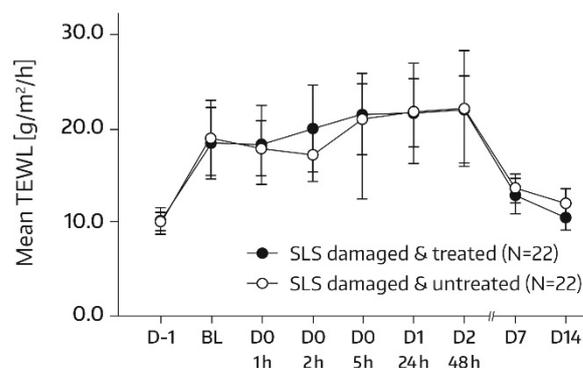

Figure 4. Results from TEWL measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 1 (first 48 h) followed by once-daily application for 12 days. The values are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment).BL = Baseline TEWL value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate.

3.1.3. Biomechanical Skin Properties (Skin Elasticity Parameters)

Table 3 summarizes the changes from baseline in skin mechanical properties (Ur/Ue and Ur/Uf) over the course of the study as assessed by cutometry in the Emollient 1-treated area (A1). For all comparisons with baseline, once-daily application of Emollient 1 induced a significant increase in the skin elasticity parameters Ur/Ue and Ur/Uf. The proportions of "positive subjects" (i.e., those who showed improved skin elasticity parameters compared with baseline, as defined in Figure 1) were 61.9, 61.9, 61.9, and 64.3% at days 7, 14, 21, and 28, respectively. In the untreated control area (A2), no increases in Ur/Ue and Ur/Uf from baseline were observed. On the contrary, a worsening was recorded in the majority of assessments (data not shown).

Table 3. Changes from baseline in elasticity parameters after single application of Emollient 1 (first 48 h) followed by once-daily application for 26 days.

	Ur/Ue	*p*-Value *	Ur/Uf	*p*-Value *
BL	0.762 ± 0.185	-	0.402 ± 0.090	-
Day 7	0.055	0.010 [§]	0.032	0.002 [§]
Day 14	0.052	0.004 [§]	0.033	0.001 [§]
Day 21	0.044	0.008 [§]	0.029	<0.001 [§]
Day 28	0.047	0.011 [§]	0.023	0.002 [§]

N = 42. The data were gathered by cutometry in area A1 (= treated with Emollient 1) and are presented as arithmetic means. BL = Baseline value (absolute mean ± SD) before first product application; Ur/Ue = net elasticity; Ur/Uf = ratio of elastic recovery to distensibility. * For mean change from baseline, paired *t*-test. [§] Significant if *p* < 0.0125 (Bonferroni correction). Note: An increase in Ur/Ue and Ur/Uf reflects improved elasticity properties of the skin.

3.1.4. SC Lipid Content

Upon treatment of skin area A0 with Emollient 1, there was a significant increase by day 28 versus baseline in mean cholesterol (9.53 ± 2.38 vs. 8.68 ± 2.54 µg/mg; 9.8%; *p* < 0.001) and mean free fatty acid levels (87.02 ± 19.29 vs. 83.95 ± 18.84 µg/mg; 3.7%;

$p = 0.030$), whereas application of Emollient 1 had no effect on mean ceramide content (25.89 ± 12.23 vs. 25.50 ± 12.41 μg/mg).

3.1.5. Tolerability

Emollient 1 applications were well tolerated. None of the subjects experienced a systemic or local AE considered to be related to the study product by the investigator. The local reactions caused by the SLS challenge (e.g., erythema) improved over the course of the study and had resolved by day 28.

3.2. *Study 2: Emollient 2—Containing an Intermediate Amount of Lipids*

In total, 42 healthy Caucasian subjects (39 females, 3 males) were enrolled and all completed the study. The mean age was 58 years (range: 20–70 years). The subgroup undergoing SLS-challenge consisted of 22 subjects.

3.2.1. SC Hydration (Corneometry)

Table 4 displays the corneometry results assessed in the Emollient 2-treated area over the course of the study, mean absolute values and mean changes from baseline of skin surface capacitance are shown. At baseline, the two skin areas treated with Emollient 2 (A1) or left untreated (A2) had comparable mean $\pm$ SD values for dryness (27.29 ± 5.23 and 25.91 ± 4.82 a.u., respectively). The single application of Emollient 2 as well as the subsequent once-daily treatment caused an increase in SC hydration as reflected by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.001$ for all comparisons with baseline). In addition, global ANOVA showed a significant difference between the skin capacitance mean value determined at baseline and subsequent measurements ($p < 0.05$). After single application, the skin-hydrating effect was most pronounced at the early measurements. On day 28, there was a 72.4% improvement in skin hydration compared with baseline (+18.24 a.u.; $p < 0.001$). In the untreated control area (A2), there was no apparent increase in SC hydration from baseline. In fact, electrical capacitance remained essentially unchanged at approximately 26–28 a.u. throughout the study. Bilateral differences between Emollient 2-treated and untreated areas, in terms of absolute mean values for skin capacitance, were significant and in favor of Emollient 2 at all postbaseline assessments (Figure 5). On day 28, the mean bilateral difference amounted to 18.60 a.u. ($p < 0.001$).

Table 4. Absolute skin capacitance measurement values and changes from baseline after single application of Emollient 2 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	27.29 ± 5.23	-	-
1 h	50.78 ± 10.59	23.49 ± 10.43	<0.001 [#]
2 h	49.35 ± 8.09	22.06 ± 7.68	<0.001 [#]
5 h	47.65 ± 10.08	20.37 ± 9.28	<0.001 [#]
24 h	38.01 ± 8.22	10.73 ± 8.07	<0.001 [#]
48 h	37.87 ± 9.41	10.58 ± 7.75	<0.001 [#]
Day 7	43.78 ± 8.06	16.50 ± 9.41	<0.001 [§]
Day 14	42.51 ± 8.88	15.23 ± 9.95	<0.001 [§]
Day 21	44.34 ± 8.33	17.05 ± 8.85	<0.001 [§]
Day 28	45.53 ± 7.93	18.24 ± 8.42	<0.001 [§]

N = 42. Data are given in a.u. The values were assessed by corneometry in area A1 (= treated with Emollient 2) and are presented as mean $\pm$ SD. BL = Baseline skin capacitance value before first product application; h = hour. * For mean change from baseline, paired *t*-test. [#] Significant if $p < 0.01$ (Bonferroni correction). [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: An increase in skin capacitance reflects a skin-hydrating effect.
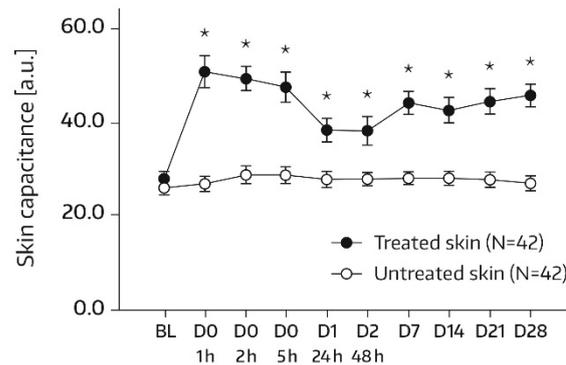
Figure 5. Results from skin capacitance measurements in untreated skin and skin undergoing a single application of Emollient 2 (first 48 h) followed by once-daily application for 26 days. The values were assessed by corneometry and are presented as mean ± SD. BL = Baseline skin capacitance value before first product application; D = day; h = hour. * $p < 0.001$ if compared to untreated control, paired *t*-test.

Likewise, in subjects of the subgroup, skin hydration increased significantly in skin that had undergone SLS-induced damage and was subsequently treated with Emollient 1. On day 14, there was a 121.0% improvement in skin hydration compared with baseline (+20.08 a.u.; $p < 0.001$). Bilateral differences between Emollient 2-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4), in terms of absolute values for skin capacitance, were significant and in favor of Emollient 2 at all postbaseline assessments (Figure 6). On day 14, the mean bilateral difference amounted to 17.02 a.u. ($p < 0.001$).
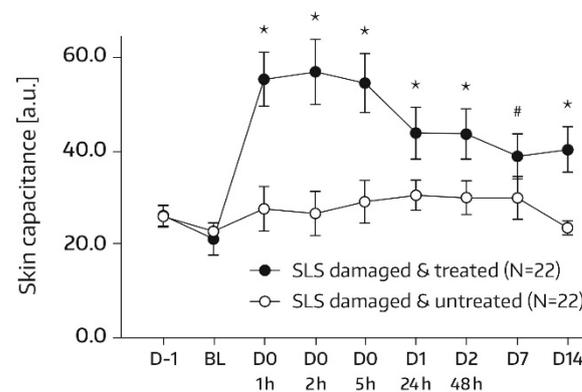

Figure 6. Results from skin capacitance measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 2 (first 48 h) followed by once-daily application for 12 days. The values were assessed by corneometry and are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment). BL = Baseline skin capacitance value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate. * $p < 0.001$ if compared to untreated control, paired *t*-test; # $p = 0.016$ if compared to untreated control, paired *t*-test.

3.2.2. Transepidermal Water Loss

Table 5 shows TEWL results assessed in the Emollient 2-treated area over the study; mean absolute values and mean changes from baseline for TEWL values are displayed. The mean TEWL baseline values were comparable between Emollient 2-treated (A1) and nontreated (A2) skin areas (9.89 ± 1.89 and 9.81 ± 1.93 g/m^2/h, respectively). Mean TEWL had decreased significantly at 1 h following first application of Emollient 2, but the effect was transient in nature. On day 28, there was a numerical decrease in TEWL of 5.7% compared with baseline (−0.62 g/m^2/h; n.s.). Bilateral differences between Emollient

2-treated and untreated areas, in terms of absolute mean values for TEWL, were not significant at all postbaseline assessments (data not shown).

Table 5. Absolute TEWL measurement values and changes from baseline after single application of Emollient 2 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	9.89 ± 1.89	-	-
1 h	8.80 ± 1.87	−1.09 ± 1.72	<0.001 [#]
2 h	9.32 ± 1.75	−0.57 ± 1.45	0.015 [#]
5 h	9.44 ± 1.58	−0.45 ± 1.17	0.017 [#]
24 h	10.64 ± 4.18	0.75 ± 4.17	0.252 [#]
48 h	12.51 ± 7.64	2.62 ± 6.85	0.017 [#]
Day 7	10.28 ± 4.74	0.40 ± 5.29	0.629 [§]
Day 14	9.65 ± 3.47	−0.24 ± 3.79	0.682 [§]
Day 21	9.09 ± 2.22	−0.80 ± 2.99	0.092 [§]
Day 28	9.27 ± 2.10	−0.62 ± 1.54	0.013 [§]

N = 42. Data are given in $g/m^2/h$. The values were assessed in area A1 (= treated with Emollient 2) and are presented as mean ± SD. BL = Baseline TEWL value before first product application; h = hour. * For mean change from baseline, paired *t*-test. [#] Significant if $p < 0.01$ (Bonferroni correction). [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: A reduction in TEWL reflects improvement in skin barrier function.

In subjects of the subgroup, the SLS challenge caused skin barrier dysfunction as reflected by an approximately 2-fold increase in TEWL at baseline compared with unchallenged test areas at day -1. By day 14, mean TEWL was close to the pre-challenge value, indicating restoration of skin barrier function. However, this applied to both treated and untreated skin. In fact, relevant bilateral differences between Emollient 2-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4) were not apparent (Figure 7).
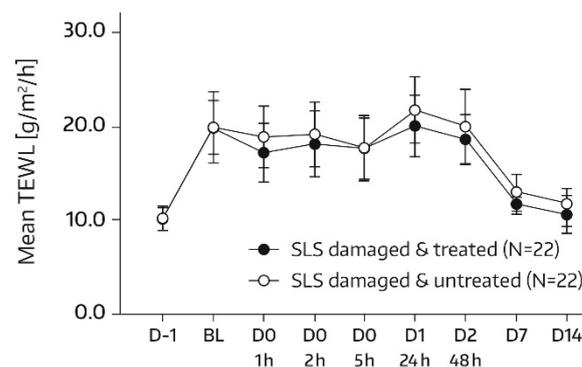

Figure 7. Results from TEWL measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 2 (first 48 h) followed by once-daily application for 12 days. The values are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment). BL = Baseline TEWL value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate.

3.2.3. Biomechanical Skin Properties (Skin Elasticity Parameters)

Table 6 summarizes the changes from baseline in skin mechanical properties (Ur/Ue and Ur/Uf) over the course of the study as assessed by cutometry in the Emollient 2-treated area (A1). For all comparisons with baseline, once-daily application of Emollient 2 induced a significant increase in the skin elasticity parameters Ur/Ue and Ur/Uf. The proportion of

"positive subjects" (i.e., those who showed improved skin elasticity parameters compared with baseline, as defined in Figure 1) was 59.5, 66.7, 73.8, and 78.6% at days 7, 14, 21, and 28, respectively. In the untreated control area (A2), Ur/Ue and Ur/Uf values remained essentially unchanged over the course of the study (data not shown).

Table 6. Changes from baseline in elasticity parameters after single application of Emollient 2 (first 48 h) followed by once-daily application for 26 days.

	Ur/Ue	*p*-Value *	Ur/Uf	*p*-Value *
BL	0.628 ± 0.128	-	0.355 ± 0.058	-
Day 7	0.073	0.001 [§]	0.034	<0.001 [§]
Day 14	0.088	<0.001 [§]	0.042	<0.001 [§]
Day 21	0.092	<0.001 [§]	0.044	<0.001 [§]
Day 28	0.135	<0.001 [§]	0.059	<0.001 [§]

N = 42. The data were gathered by cutometry in area A1 (= treated with Emollient 2) and are presented as arithmetic means. BL = Baseline value (absolute mean ± SD) before first product application; Ur/Ue = net elasticity; Ur/Uf = ratio of elastic recovery to distensibility. * For mean change from baseline, paired *t*-test. [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: An increase in Ur/Ue and Ur/Uf reflects improved elasticity properties of the skin.

3.2.4. SC Lipid Content

Application of Emollient 2 to skin area A0 had no effect on ceramides, cholesterol, or free fatty acids levels of the SC (data not shown).

3.2.5. Tolerability

Emollient 2 applications were well tolerated. None of the subjects experienced a systemic or local AE considered to be related to the study product by the investigator. The local reactions caused by the SLS challenge (e.g., erythema) improved over the course of the study and had resolved by day 28.

3.3. Study 3: Emollient 3—Containing the Highest Amount of Lipids

In total, 42 healthy Caucasian subjects (40 females, 2 males) were enrolled and almost all completed the study according to protocol. One subject missed the day-28 visit. The mean age was 57 years (range: 27–62 years). The subgroup undergoing SLS-challenge consisted of 22 subjects.

3.3.1. SC Hydration (Corneometry)

At baseline, the two skin areas treated with Emollient 3 (A1) or left untreated (A2) had comparable mean ± SD values for dryness (29.35 ± 5.93 and 28.41 ± 5.34 a.u., respectively). Table 7 displays the corneometry results assessed in the Emollient 3-treated area over the course of the study, mean absolute values and mean changes from baseline of skin surface capacitance are shown. The single application of Emollient 3 as well as the subsequent once-daily treatment induced an increase in SC hydration as mirrored by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.001$ for all comparisons with baseline). In addition, global ANOVA revealed a significant difference between the skin capacitance mean value determined at baseline and subsequent measurements ($p < 0.05$). After single application, the skin-hydrating effect was most pronounced at the early measurements but was still apparent after 48 h. On day 28, there was a 38.1% improvement in skin hydration compared with baseline (+9.95 a.u.; $p < 0.001$) considering subjects evaluable for both assessment times (N = 41). In the untreated control area (A2), no increase in SC hydration from baseline was observed. In fact, electrical capacitance remained essentially unchanged at approximately 28–31 a.u. throughout the study. Bilateral differences between Emollient 3-treated and untreated areas, in terms of absolute mean values for skin capacitance, were significant and in favor of Emollient 3 at all postbaseline

assessments (Figure 8). On day 28, the mean bilateral difference amounted to 8.94 a.u. ($p < 0.001$).

Table 7. Absolute skin capacitance measurement values and changes from baseline after single application of Emollient 3 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	29.35 ± 5.93	-	-
1 h	49.15 ± 9.88	19.80 ± 8.91	<0.001 [#]
2 h	46.36 ± 7.83	17.01 ± 8.00	<0.001 [#]
5 h	48.96 ± 10.67	19.61 ± 8.42	<0.001 [#]
24 h	36.99 ± 6.80	7.60 ± 7.06	<0.001 [#]
48 h	38.84 ± 10.04	9.49 ± 9.42	<0.001 [#]
Day 7	40.15 ± 7.68	10.67 ± 8.10	<0.001 [§]
Day 14	39.58 ± 9.28	10.37 ± 9.62	<0.001 [§]
Day 21	40.07 ± 8.88	10.86 ± 9.69	<0.001 [§]
Day 28	39.15 ± 8.62	9.95 ± 9.24	<0.001 [§]

N = 40–42. Data are given in a.u. The values were assessed by corneometry in area A1 (= treated with Emollient 3) and are presented as mean $\pm$ SD. BL = Baseline skin capacitance value before first product application; h = hour. * For mean change from baseline, paired *t*-test. [#] Significant if $p < 0.01$ (Bonferroni correction). [§] Significant if $p < 0.0125$ (Bonferroni correction). Note: An increase in skin capacitance reflects a skin-hydrating effect.
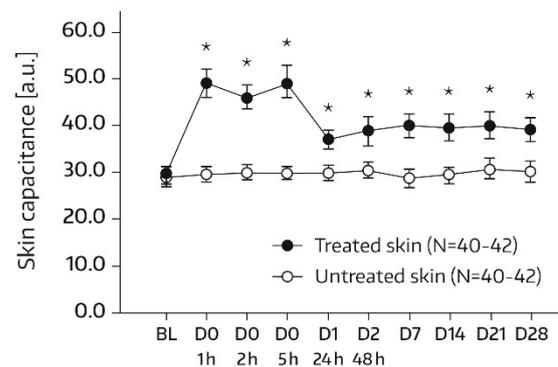

Figure 8. Results from skin capacitance measurements in untreated skin and skin undergoing a single application of Emollient 3 (first 48 h) followed by once-daily application for 26 days. The values were assessed by corneometry and are presented as mean $\pm$ SD. BL = Baseline skin capacitance value before first product application; D = day; h = hour. * $p < 0.001$ if compared to untreated control, paired *t*-test.

Similarly, in subjects of the subgroup, skin hydration increased significantly in skin that had undergone SLS-induced damage and was subsequently treated with Emollient 3. On day 14, there was a 58.1% improvement in skin hydration compared with baseline (+14.55 a.u.; $p < 0.001$) considering subjects evaluable for both assessment times (N = 21). Bilateral differences between Emollient 3-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4), in terms of absolute values for skin capacitance, were significant and in favor of Emollient 3 at all postbaseline assessments (Figure 9). On day 14, the mean bilateral difference amounted to 13.92 a.u. ($p < 0.001$).
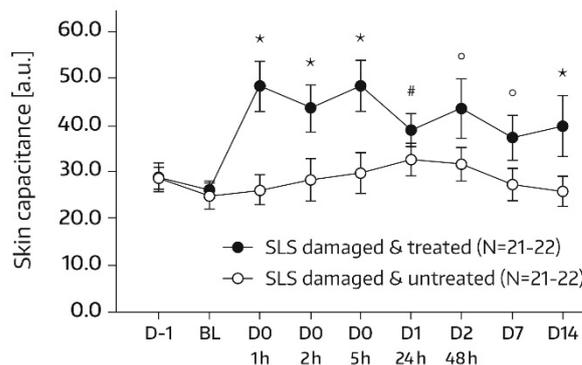
Figure 9. Results from skin capacitance measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 3 (first 48 h) followed by once-daily application for 12 days. The values were assessed by corneometry and are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment). BL = Baseline skin capacitance value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate. * $p < 0.001$ if compared to untreated control, paired *t*-test. # $p = 0.018$ if compared to untreated control, paired *t*-test. ° $p = 0.001$ if compared to untreated control, paired *t*-test.

3.3.2. Transepidermal Water Loss

The mean TEWL baseline values were comparable between Emollient 3-treated (A1) and nontreated (A2) skin areas (9.44 ± 3.26 and 8.75 ± 2.64 g/m^2/h, respectively]. Table 8 shows TEWL results assessed in the Emollient 3-treated area over the study, mean absolute values and mean changes from baseline for TEWL values are displayed. Mean TEWL had decreased significantly at 1 h following first application of Emollient 3. The effect was transient in nature. On day 28, there was a numerical decrease in TEWL compared with baseline (-0.44 g/m^2/h; n.s.). Bilateral differences between Emollient 3-treated and untreated areas, in terms of absolute mean values for TEWL, were not significant at all postbaseline assessments (data not shown).

Table 8. Absolute TEWL measurement values and changes from baseline after single application of Emollient 3 (first 48 h) followed by once-daily application for 26 days.

	Absolute Value	Change from BL	*p*-Value *
BL	9.44 ± 3.26	-	-
1 h	8.03 ± 1.69	−1.41 ± 2.91	0.003 #
2 h	8.26 ± 1.53	−1.18 ± 3.28	0.024 #
5 h	8.90 ± 6.45	−0.55 ± 7.53	0.641 #
24 h	9.60 ± 4.33	0.17 ± 4.11	0.789 #
48 h	11.58 ± 6.46	2.14 ± 6.25	0.032 #
Day 7	10.86 ± 6.45	1.33 ± 6.06	0.168 §
Day 14	10.62 ± 4.35	1.09 ± 5.33	0.196 §
Day 21	9.50 ± 2.54	−0.03 ± 4.39	0.967 §
Day 28	9.09 ± 2.79	−0.44 ± 4.03	0.486 §

N = 41–42. Data are given in g/m^2/h. The values were assessed in area A1 (= treated with Emollient 3) and are presented as mean ± SD. BL = Baseline TEWL value before first product application; h = hour. * For mean change from baseline, paired *t*-test. # Significant if $p < 0.01$ (Bonferroni correction). § Significant if $p < 0.0125$ (Bonferroni correction). Note: A reduction in TEWL reflects improvement in skin barrier function.

In subjects of the subgroup, the SLS challenge caused skin barrier dysfunction as reflected by an approximately 2-fold increase in TEWL at baseline compared with un-challenged test areas at day -1. By day 14, mean TEWL reached the prechallenge level,

indicating restoration of skin barrier function. However, this applied to both treated and untreated skin. In fact, no relevant bilateral differences between Emollient 3-treated SLS-damaged skin area (A3) and the untreated SLS-damaged skin area (A4) were observed (Figure 10).
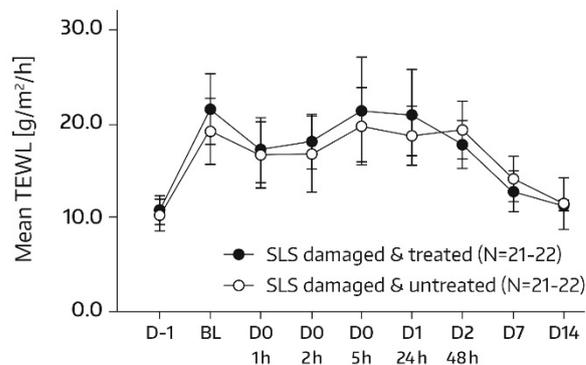

Figure 10. Results from TEWL measurements in untreated SLS-damaged skin and SLS-damaged skin undergoing a single application of Emollient 3 (first 48 h) followed by once-daily application for 12 days. The values are presented as mean ± SD. SLS challenge started on day -1 and ceased 24 h later (30 min before BL assessment). BL = Baseline TEWL value before first product application; D = day; h = hour; SLS = sodium lauryl sulfate.

3.3.3. Biomechanical Skin Properties (Skin Elasticity Parameters)

Table 9 summarizes the changes from baseline in skin mechanical properties (Ur/Ue and Ur/Uf) over the course of the study, as assessed by cutometry in the Emollient 3-treated area (A1). For all comparisons with baseline, once-daily application of Emollient 3 produced a significant increase in the skin elasticity parameters Ur/Ue and Ur/Uf. The proportion of "positive subjects" (i.e., those who showed improved skin elasticity parameters compared with baseline, as defined in Figure 1) was 65.9, 68.3, 73.2, and 80.5% at days 7, 14, 21, and 28, respectively. In the untreated control area (A2), Ur/Ue and Ur/Uf values remained virtually unchanged over the course of the study (data not shown).

Table 9. Changes from baseline in elasticity parameters after single application of Emollient 3 (first 48 h) followed by once-daily application for 26 days.

	Ur/Ue	*p*-Value *	Ur/Uf	*p*-Value *
BL	0.522 ± 0.160	–	0.309 ± 0.079	–
Day 7	0.062	0.003 [§]	0.037	<0.001 [§]
Day 14	0.093	<0.001 [§]	0.046	<0.001 [§]
Day 21	0.110	<0.001 [§]	0.055	<0.001 [§]
Day 28	0.127	<0.001 [§]	0.068	<0.001 [§]

N = 41. The data were gathered by cutometry in area A1 (= treated with Emollient 3) and are presented as arithmetic means. BL = Baseline value (absolute mean ± SD) before first product application; Ur/Ue = net elasticity; Ur/Uf = ratio of elastic recovery to distensibility. * For mean change from baseline, paired *t*-test. [§] Significant if *p* < 0.0125 (Bonferroni correction). Note: An increase in Ur/Ue and Ur/Uf reflects improved elasticity properties of the skin.

3.3.4. SC Lipid Content

Upon treatment of skin area A0 with Emollient 3, there was a significant increase by day 28 vs. baseline in mean cholesterol (6.13 ± 2.62 vs. 5.45 ± 2.57 µg/mg; 12.5%; *p* = 0.045) and mean free fatty acid levels (102.50 ± 36.89 vs. 81.13 ± 23.40 µg/mg; 26.3%; *p* < 0.001), whereas application of Emollient 3 had no significant effect on mean ceramide content (37.40 ± 19.74 vs. 34.44 ± 16.62 µg/mg; 8.6%; *p* = 0.158).

3.3.5. Tolerability

Emollient 3 applications were well tolerated. None of the subjects experienced a systemic or local AE considered to be related to the study product by the investigator. The local reactions caused by the SLS challenge (e.g., erythema) improved over the course of the study and were resolved by day 28.

4. Discussion

Three new topical dexpanthenol-containing emollients with different lipid contents (Emollients 1–3) were developed for subjects with dry skin conditions. In this context, three studies explored their effects on SC hydration, TEWL, skin biomechanical properties, and SC lipid content as well as their cutaneous tolerability after single and continued once-daily application. The present studies are the first providing data on the performance and tolerability of the new topical dexpanthenol-containing emollient line in subjects with dry skin.

If compared with contralateral skin areas and/or baseline assessments, the study results may be summarized as follows: (1) following a single application of Emollients 1–3 to dry skin and dry SLS-damaged skin, skin capacitance was significantly increased for up to 48 h indicating long-lasting skin hydration; (2) after once-daily application of Emollients 1–3 to dry skin and dry SLS-damaged skin for approximately 4 and 2 weeks, respectively, skin capacitance was significantly increased in all assessments suggesting long-term hydration; (3) following single and prolonged once-daily application of Emollients 1–3 to dry skin and dry SLS-damaged skin for approximately 4 and 2 weeks, respectively, no sustained effects on TEWL were recorded—the effects were transient in nature; (4) all three emollients induced a significant increase in skin elasticity parameters upon prolonged once-daily use; (5) the once-daily usage of Emollient 1 and Emollient 3 was associated with a significant increase in cholesterol and free fatty acid levels in the SC; (6) all three emollients showed a favorable cutaneous tolerability.

All three emollients showed a good performance in the selected population with only minor differences in a few results from instrumental or lipid content measurements. In particular, they were all effective skin moisturizers as requested for state-of-the-art emollients. The observed skin-hydrating effects were in accordance with previous studies using an emollient with a similar composition [13,14]. Based on recent evidence, it may be inferred that the favorable effects on skin hydration mediated by Emollients 1–3 are induced by their key ingredients which act in an additive/synergistic way. Glycerin reaches deeper layers of the SC where it restores water content and replicates the function of natural moisturizing factors [1]. Dexpanthenol interacts with lipid segments of the extracellular lamellae and protein residues in the SC corneocytes and increases molecular mobility/fluidity [9,26]. By this mechanism, it compensates for reduced hydration and reduces the increased rigidity of the SC lipid lamellae and keratin filaments observed in dry skin; in addition, dexpanthenol acts as a humectant [1]. Typically, dry skin is lipid-depleted [27,28]. The nonphysiological and physiological lipids present in Emollients 1–3 act as substitutes for the lost natural skin lipids and improve the water-binding capacity of the SC [14]. In addition, nonphysiological lipids largely stay on the SC surface and provide hydrating effects by working as a temporary dressing [1].

None of the tested emollients showed a sustained effect on TEWL. In particular, no differences in skin barrier recovery were observed between treated and untreated SLS-damaged skin. This is in contradiction to a previous study using an emollient with a similar composition [13]. In that study, following a sodium dodecylsulfate solution (SDS) challenge, recovery of the skin barrier (i.e., decrease in TEWL) was more pronounced in the skin area treated with the study product compared with the untreated area on the contralateral volar forearm. The observed increase in TEWL after SDS challenge was 3-fold compared to a 2-fold increase after SLS challenge in our studies. In addition, it took approximately 3 weeks until TEWL of the untreated SDS-damaged skin had normalized, while in our studies, TEWL had reached or was close to prechallenge levels after 1 to 2 weeks already.

Hence, it could be that in our studies the experimentally induced skin barrier dysfunction was too mild to be discriminatory. Spontaneous healing of 0.8% SLS-damaged skin might have been too fast to detect differences in TEWL changes between treated and untreated skin areas. In fact, it has been suggested that higher SLS concentrations are needed to induce mild to moderate skin reactions in healthy subjects [29].

It has been previously shown that emollients are able of inducing significant changes in the biomechanical properties of skin and that the SC plays an important role in skin mechanics [30]. In fact, the stiffness and firmness of the SC is mainly influenced by its moisturization status, with increasing firmness as the water content decreases [31,32]. This is in accordance with the findings of our studies. The skin-hydrating effects induced by all three emollients were paralleled by significant increases in skin elasticity parameters which is a desired feature of cosmetic skin care products.

The intercellular lipid matrix of the SC consists mainly of ceramides, cholesterol, and free fatty acids; these are required for adequate SC hydration [33,34]. In dry skin conditions, the SC lipid quantities are reduced and the lipid composition/organization is altered. For example, it was shown that the SC quantities of ceramides, cholesterol, and free fatty acids are reduced during winter (when the skin is dry) compared with the summer period [1]. In our studies, we observed a significant increase in SC cholesterol and SC free fatty acid levels upon prolonged use of Emollient 1 and Emollient 3. This can be attributed to the presence of niacinamide in these emollients. It is known that niacinamide increases the biosynthesis of natural SC lipids [7,35]. Our finding is in agreement with a previous healthy volunteer study using another niacinamide-containing emollient [13]. In that 4-week study, the study product induced a significant increase in cholesterol and free fatty acids levels in the SC. The reason why, in the present study, Emollient 2 showed no effect on SC lipids, although it contains a similar lipid composition, remains to be elucidated.

In our trials, all three emollients were well tolerated which is in accordance with previous studies conducted with emollients [36].

A limitation of our three studies is that an untreated control was used instead of applying a placebo formulation. However, considering the complex composition of Emollients 1–3, it was not possible to control for all ingredients considered important for the desired effects. Another limitation of our study is the absence of a control skin area for quantification of SC lipids. Hence, we could not account for spontaneous changes in SC lipid content over the 4-week study periods.

5. Conclusions

The results of our three studies suggest that the single and prolonged once-daily application of Emollients 1–3 is associated with significant skin-hydrating effects which are paralleled by significant increases in skin elasticity parameters. Results from lipid analyses imply that Emollients 1 and 3 exert favorable effects on some natural skin lipids in the outer layers of the SC. In addition, Emollients 1–3 were well tolerated by healthy subjects with dry skin in these 4-week studies. Our findings support the once-daily use of all three emollients in adult subjects with dry skin. Since only minor differences in a few results from instrumental or lipid content measurements were observed, the choice between the tested oil-in-water emulsion formulations can be based on personal preferences.

References

1. Proksch, E.; Berardesca, E.; Misery, L.; Engblom, J.; Bouwstra, J. Dry skin management: Practical approach in light of latest research on skin structure and function. *J. Dermatol. Treat.* **2020**, *31*, 716–722. [CrossRef] [PubMed]
2. Augustin, M.; Kirsten, N.; Körber, A.; Wilsmann-Theis, D.; Itschert, G.; Staubach-Renz, P.; Maul, J.; Zander, N. Prevalence, predictors and comorbidity of dry skin in the general population. *J. Eur. Acad. Dermatol. Venereol.* **2019**, *33*, 147–150. [CrossRef] [PubMed]
3. Giménez-Arnau, A. Standards for the Protection of Skin Barrier Function. *Curr. Probl. Dermatol.* **2016**, *49*, 123–134. [CrossRef] [PubMed]
4. Yosipovitch, G.; Misery, L.; Proksch, E.; Metz, M.; Ständer, S.; Schmelz, M. Skin Barrier Damage and Itch: Review of Mechanisms, Topical Management and Future Directions. *Acta Derm. Venereol.* **2019**, *99*, 1201–1209. [CrossRef]
5. Proksch, E.; Lachapelle, J.-M. The management of dry skin with topical emollients—Recent perspectives. Behandlung der trockenen Haut mit topischen Emulsionen—Neue Entwicklungen. *J. Dtsch. Dermatol. Ges.* **2005**, *3*, 768–774. [CrossRef]
6. Fluhr, J.; Darlenski, R.; Surber, C. Glycerol and the skin: Holistic approach to its origin and functions. *Br. J. Dermatol.* **2008**, *159*, 23–34. [CrossRef]
7. Otte, N.; Borelli, C.; Korting, H.C. Nicotinamide—Biologic actions of an emerging cosmetic ingredient. *Int. J. Cosmet. Sci.* **2005**, *27*, 255–261. [CrossRef]
8. Wohlrab, J.; Kreft, D. Niacinamide—Mechanisms of Action and Its Topical Use in Dermatology. *Skin Pharmacol. Physiol.* **2014**, *27*, 311–315. [CrossRef]
9. Proksch, E.; De Bony, R.; Trapp, S.; Boudon, S. Topical use of dexpanthenol: A 70th anniversary article. *J. Dermatol. Treat.* **2017**, *28*, 766–773. [CrossRef]
10. Lin, T.-K.; Zhong, L.; Santiago, J.L. Anti-Inflammatory and Skin Barrier Repair Effects of Topical Application of Some Plant Oils. *Int. J. Mol. Sci.* **2017**, *19*, 70. [CrossRef] [PubMed]
11. Duffy, E.; Jacobs, M.R.; Kirby, B.; Morrin, A. Probing skin physiology through the volatile footprint: Discriminating volatile emissions before and after acute barrier disruption. *Exp. Dermatol.* **2017**, *26*, 919–925. [CrossRef] [PubMed]
12. Caussin, J.; Gooris, G.S.; Bouwstra, J.A. FTIR studies show lipophilic moisturizers to interact with stratum corneum lipids, rendering the more densely packed. *Biochim. Biophys. Acta (BBA) Biomembr.* **2008**, *1778*, 1517–1524. [CrossRef]
13. Stettler, H.; Kurka, P.; Lunau, N.; Manger, C.; Böhling, A.; Bielfeldt, S.; Wilhelm, K.-P.; Dähnhardt-Pfeiffer, S.; Dähnhardt, D.; Brill, F.H.; et al. A new topical panthenol-containing emollient: Results from two randomized controlled studies assessing its skin moisturization and barrier restoration potential, and the effect on skin microflora. *J. Dermatol. Treat.* **2017**, *28*, 173–180. [CrossRef] [PubMed]
14. Stettler, H.; Kurka, P.; Wagner, C.; Sznurkowska, K.; Czernicka, O.; Böhling, A.; Bielfeldt, S.; Wilhelm, K.-P.; Lenz, H. A new topical panthenol-containing emollient: Skin-moisturizing effect following single and prolonged usage in healthy adults, and tolerability in healthy infants. *J. Dermatol. Treat.* **2017**, *28*, 251–257. [CrossRef]
15. Fitzpatrick, T.B. The validity and practicality of sun-reactive skin types I through VI. *Arch. Dermatol.* **1988**, *124*, 869–871. [CrossRef]
16. Clarys, P.; Clijsen, R.; Taeymans, J.; Barel, A.O. Hydration measurements of the stratum corneum: Comparison between the capacitance method (digital version of the Corneometer CM 825®) and the impedance method (Skicon-200EX®). *Skin Res. Technol.* **2012**, *18*, 316–323. [CrossRef]
17. Heinrich, U.; Koop, U.; Leneveu-Duchemin, M.-C.; Osterrieder, K.; Bielfeldt, S.; Chkarnat, C.; Degwert, J.; Hantschel, D.; Jaspers, S.; Nissen, H.-P.; et al. Multicentre comparison of skin hydration in terms of physical-, physiological- and product-dependent parameters by the capacitive method (Corneometer CM 825). *Int. J. Cosmet. Sci.* **2003**, *25*, 45–53. [CrossRef] [PubMed]
18. Pinnagoda, J.; Tupker, R.A.; Agner, T.; Serup, J. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermat.* **1990**, *22*, 164–178. [CrossRef]
19. Antonov, D.; Schliemann, S.; Elsner, P. Methods for the Assessment of Barrier Function. *Sex. Transm. Dis. Adv. Diagn. Treat.* **2016**, *49*, 61–70. [CrossRef]
20. Dobrev, H. Use of Cutometer to assess epidermal hydration. *Skin Res. Technol.* **2000**, *6*, 239–244. [CrossRef] [PubMed]

21. Ryu, H.S.; Joo, Y.H.; Kim, S.O.; Park, K.C.; Youn, S.W. Influence of age and regional differences on skin elasticity as measured by the Cutometer. *Skin Res. Technol.* **2008**, *14*, 354–358. [CrossRef]

22. Krueger, N.; Luebberding, S.; Oltmer, M.; Streker, M.; Kerscher, M. Age-related changes in skin mechanical properties: A quantitative evaluation of 120 female subjects. *Skin Res. Technol.* **2011**, *17*, 141–148. [CrossRef]

23. Luebberding, S.; Krueger, N.; Kerscher, M. Mechanical properties of human skin in vivo: A comparative evaluation in 300 men and women. *Skin Res. Technol.* **2014**, *20*, 127–135. [CrossRef] [PubMed]

24. Yimam, M.; Lee, Y.-C.; Jiao, P.; Hong, M.; Brownell, L.; Jia, Q. A Randomized, Active Comparator-controlled Clinical Trial of a Topical Botanical Cream for Skin Hydration, Elasticity, Firmness, and Cellulite. *J. Clin. Aesthetic Dermatol.* **2018**, *11*, 51–57.

25. Combarros, D.; Castilla-Castaño, E.; Lecru, L.; Pressanti, C.; Amalric, N.; Cadiergues, M.C. A prospective, randomized, double blind, placebo-controlled evaluation of the effects of an n-3 essential fatty acids supplement (Agepi® ω3) on clinical signs, and fatty acid concentrations in the erythrocyte membrane, hair shafts and skin surface of dogs with poor quality coats. *Prostaglandins Leukot. Essent. Fat. Acids* **2020**, *159*. [CrossRef]

26. Björklund, S.; Pham, Q.D.; Jensen, L.B.; Knudsen, N.Ø.; Nielsen, L.D.; Ekelund, K.; Ruzgas, T.; Engblom, J.; Sparr, E. The effects of polar excipients transcutol and dexpanthenol on molecular mobility, permeability, and electrical impedance of the skin barrier. *J. Colloid Interface Sci.* **2016**, *479*, 207–220. [CrossRef] [PubMed]

27. Imokawa, G.; Abe, A.; Jin, K.; Higaki, Y.; Kawashima, M.; Hidano, A. Decreased Level of Ceramides in Stratum Corneum of Atopic Dermatitis: An Etiologic Factor in Atopic Dry Skin? *J. Investig. Dermatol.* **1991**, *96*, 523–526. [CrossRef]

28. van Smeden, J.; Bouwstra, J.A. Stratum corneum lipids: Their role for the skin barrier function in healthy subjects and atopic dermatitis patients. *Curr. Probl. Dermatol.* **2016**, *49*, 8–26.

29. Willis, C.M.; Stephens, C.J.M.; Wilkinson, J.D. Experimentally-induced irritant contact dermatitis. Determination of optimum irritant concentrations. *Contact Dermat.* **1988**, *18*, 20–24. [CrossRef] [PubMed]

30. Overgaard Olsen, L.; Jemec, G.B. The influence of water, glycerin, paraffin oil and ethanol on skin mechanics. *Acta Derm. Venereol.* **1993**, *73*, 404–406.

31. Sakai, S.; Sasai, S.; Endo, Y.; Matue, K.; Tagami, H.; Inoue, S. Characterization of the physical properties of the stratum corneum by a new tactile sensor. *Skin Res. Technol.* **2000**, *6*, 128–134. [CrossRef] [PubMed]

32. Paye, M.; Mac-Mary, S.; Elkhyat, A.; Tarrit, C.; Mermet, P.; Humbert, P.H. Use of the Reviscometer® for measuring cosmetics-induced skin surface effects. *Skin Res. Technol.* **2007**, *13*, 343–349. [CrossRef] [PubMed]

33. Proksch, E.; Brandner, J.M.; Jensen, J.-M. The skin: An indispensable barrier. *Exp. Dermatol.* **2008**, *17*, 1063–1072. [CrossRef] [PubMed]

34. van Smeden, J.; Janssens, M.; Gooris, G.S.; Bouwstra, J.A. The important role of stratum corneum lipids for the cutaneous barrier function. *Biochim. Biophys. Acta* **2014**, *1841*, 295–313. [CrossRef] [PubMed]

35. Tanno, O.; Ota, Y.; Kitamura, N.; Katsube, T.; Inoue, S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br. J. Dermatol.* **2000**, *143*, 524–531. [CrossRef] [PubMed]

36. Lodén, M. Treatments Improving Skin Barrier Function. *Curr. Probl. Dermatol.* **2016**, *49*, 112–122. [CrossRef]