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Three New Dexpanthenol-Containing Face Creams: Performance and Acceptability after Single and Repeated Applications in Subjects of Different Ethnicity with Dry and Sensitive Skin

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Abstract: Three novel face creams containing dexpanthenol with different lipid contents were developed for dry skin sufferers: a day face cream (DFC), a day face cream with sun protection (DFC-SPF), and a night face cream (NFC). Three identically designed studies (N = 42–44 each) were conducted with healthy adults of three ethnicities (African, Asian, Caucasian) with dry/sensitive skin. Effects on stratum corneum (SC) hydration, SC lipid content, and skin elasticity were quantified by established noninvasive methods during the 4-week studies. After single and repeated once-daily applications of the face creams, facial hydration significantly increased from baseline. On day 28, the mean increments in skin hydration amounted to 27%, 26%, and 27% ($p < 0.0001$ each) for DFC, DFC-SPF, and NFC, respectively. Favorable effects of DFC, DFC-SPF, and NFC on facial moisturization were observed in all three ethnic groups. The enhancements in SC hydration were not paralleled by improvements in skin elasticity parameters but lipid analyses showed significant increases in SC cholesterol, SC free fatty acid, and/or SC ceramide levels. All three face creams were well tolerated and achieved a high product satisfaction and acceptability by study participants. Our findings support the once-daily use of the face creams in adults of different ethnicities with dry and sensitive skin.

Keywords: dexpanthenol; dry skin; ethnicity; face cream; moisturization; study; xerosis

1. Introduction

Frequently, xerotic skin is accompanied by impaired quality of life and reduced self-esteem, particularly when the face is involved [1,2]. In comparison with other body locations, facial skin is thinner. In fact, facial SC has only 7–10 cell layers, while the forearm has approximately 15–20 cell layers [3]. At the same time, the skin of the face is continuously exposed to environmental challenges (e.g., cold/hot weather, pollution, UV rays) [2,4]. This makes the skin on the face particularly prone to dryness [5].

Hydration of the skin helps to improve dryness and associated symptoms [6]. In fact, previous studies showed that moisturizers or emollients increase skin surface hydration and alleviate dry skin symptoms, but their effectiveness depends on their composition [4,7,8]. Specifically, there is still an unmet need for facial moisturizers satisfying consumers of different ethnicities [3]. Skin capacitance, which is a function of the SC water content [9], and transepidermal water loss (TEWL) vary on different parts of the face, and the skin

capacitance and TEWL gradients within short distances on selected areas of the face are distinctive in different ethnic groups [3,10]. A study in healthy young female volunteers representing four ethnic groups showed that skin hydration is greatest for Black Africans, followed by Indians, Caucasians, and Chinese [10]. It is, therefore, not surprising that the performance of facial moisturizers may reveal ethnic differences. It has been suggested that the latter is related to underlying skin biochemistry and/or ethnic differences in product application [3], with the caveat that there is a general paucity of data from intrastudy comparisons on the effects of moisturizers on facial skin hydration in different ethnic groups.

With that in mind, three new dexpanthenol-containing face creams for daily application (Bepanthen® (Bayer Consumer Care, Basel, Switzerland) Derma Replenishing Daily Moisture Face Cream (DFC), Bepanthen® Derma Restoring Daily Face Cream with SPF25 (DFC-SPF), and Bepanthen® Derma Regenerating Night Face Cream (NFC)) were developed for dry skin sufferers. All three face creams are based on the same chassis. Key ingredients are identical in the three preparations and comprise dexpanthenol (2.5%), shea butter, argan oil, squalane, niacinamide (2%), glycerin, and isopropyl isostearate; the composition is also called "repair complex". The preparations show a different lipid content (i.e., squalane, shea butter, and isopropyl isostearate), with NFC showing the highest and DFC-SPF the lowest amount of lipids. DFC has an intermediate lipid content. DFC-SPF was developed to not only provide the potential for SC hydration but also to protect from UV rays. DFC-SPF contains multiple UV filters to achieve a sun protection factor (SPF) of 25 (i.e., 96% of UVB rays that meet the skin are blocked). The PF against UVA is 9.19, and the SPF/UVA PF ratio amounts to 2.72.

DFC, DFC-SPF, and NFC contain no silicone and no fragrance.

It has been suggested that an ideal emollient should contain the following five key ingredients: physiological lipids, nonphysiological lipids, humectants, antipruritics/soothing agents, and agents that support epidermal differentiation [1]. This was considered in the development of DFC, DFC-SPF, and NFC. The new face creams contain nonphysiological lipids (argan oil, shea butter, squalane), a physiological lipid (isopropyl isostearate), a humectant (glycerin), an antipruritic/soothing agent (niacinamide), and a multifunctional ingredient including the enhancement of epidermal differentiation (dexpanthenol) [11–14].

The objective of our trials was to investigate whether all of the new face creams are suitable for the daily face care (day and night) of dry/sensitive skin sufferers. For that purpose, the performance, cutaneous tolerability, product satisfaction, and acceptability of DFC, DFC-SPF, and NFC were explored in three independent 4-week studies involving healthy adult subjects of three ethnicities (African, Asian, Caucasian) with dry and sensitive skin. Effects on SC hydration, SC lipid content, and skin elasticity were quantified by established experimental noninvasive methods over the study course. Product satisfaction and acceptability were assessed by means of a questionnaire and a scoring system, respectively. All three studies followed the same design.

2. Methods

The three studies were conducted in healthy adult subjects with dry and sensitive skin under the supervision of dermatologists at Eurofins Dermscan, Villeurbanne, France, and Insight Research, Quarte-Bornes, Mauritius, between September 2019 and February 2020. The trials were performed in accordance with the Declaration of Helsinki with all its amendments, Good Clinical Practice, and local regulatory requirements. Subjects gave written informed consent to participate after being informed about study procedures, and they consented that the photographs of their faces may be used in publications. Bayer Consumer Care AG, Basel, Switzerland, provided the face creams applied in the trials.

No formal sample size calculation was performed, given the exploratory manner of the three studies. For the same reason, no primary and secondary variables were defined. It was planned to enroll 42 subjects, with 14 subjects per ethnicity. In each center, study participants were assigned to ethnic groups in a nonrandomized fashion; no stratification by

center took place. Based on the experience with similar cosmetic studies, it was anticipated that scientifically sound results can be retrieved with the planned sample size [15–17].

2.1. Study 1: DFC—Day Face Cream

2.1.1. Study Design

Study 1 was a 2-center, open-label, intraindividual comparison study in adult healthy volunteers with dry and sensitive skin. Every subject served as their own control. Subjects of three ethnicities (African, Asian, Caucasian) were recruited. After checking eligibility for study participation at screening, study visits were scheduled for day 0 (baseline) and days 1, 2, 7, 14, 21, and 28. Subjects were asked to come to the trial center without having applied DFC that day.

The subjects had various test areas in the face. Approximately 0.5 g of DFC was to be applied once daily on the entire face by slight massage. Then, the cream was left on the facial skin without rinsing or wiping. The applications during study visits were conducted with the support of a technician. All other DFC administrations were performed by the subjects at home every morning until day 28. DFC treatment started on day 0 after the baseline assessments were completed. No DFC was applied within the first 48 h after initial application. Compliance was assured by weighing each container with DFC (50 mL) before and after cessation of the treatment period.

2.1.2. Subjects

Healthy female and male subjects of African (Fitzpatrick skin types IV–V), Asian (Fitzpatrick skin types II–IV), or Caucasian (Fitzpatrick skin types II–IV) ethnicity aged between 18 and 50 years were eligible for the study [18]. Subjects were required to have sensitive and dry facial skin, corresponding to a corneometer value of less than 50 arbitrary units (a.u.), as assessed by measurements on the cheekbones and jawlines. The existence of sensitive skin was determined by a questionnaire including presence of unpleasant sensations (signs) due to specific stimuli (factors), and times of occurrence (frequency). The questionnaire followed the French requirements to identify sensitive skin [19]. 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 from study participation if they had any skin pathology or condition at the face application areas that would interfere with interpretation of study results (e.g., eczema, atopic skin, acne, pronounced pilosity, tattoo); a severe or progressive disease or any other systemic pathology that may interfere with study outcomes; history of allergy to cosmetic/health care topical products; allergy to any ingredient of the study product; a condition requiring any topical or systemic treatment interfering with study assessments within the previous weeks prior to the trial; or intensive exposure to sunlight or UV rays within the previous month before study start and/or foreseen during the study.

Study participants were not allowed to change their lifestyle habits over the study period. Specifically, they were requested to continue to use their usual hygiene and care products but were asked not to change the brand or use new products throughout the course of the study. Subjects applying DFC or DFC-SPF were allowed to use their usual night cream, while subjects applying NFC were allowed to use their usual day cream. In addition, sunbathing, visits at tanning solariums, and the use of tanning creams were not permitted over the study course. On visit days at the study site, subjects had to come to the trial center without having applied any product on the face and without having washed or moistened their face since the previous evening. Similarly, study participants were requested not to wash or moisten their face within the first 48 h after initial application. Male subjects were asked to come to the investigational site with their facial hair shaved the previous morning.

2.1.3. Assessments

SC hydration was measured via a corneometer (Corneometer® CM825, Courage & Khazaka, Cologne, Germany), which determines the electrical capacitance of the skin surface [20]. Measurements were performed on 30 predefined facial sites distributed over one side of the face, as reported previously [10]. The determinations took place at baseline and at 24 h (day 1) and 48 h (day 2) after the first and single application of DFC. Additional assessments took place on study days 7, 14, 21, and 28. Three measurements were conducted in each test area per assessment time.

To visualize and illustrate the moisturizing effects of DFC, the whole face continuous color mapping approach was pursued [3,10]. For that purpose, a full face macrophotograph was taken from each subject by means of VISIA® CAS (Canfield Scientific, Inc., Parsippany-Troy Hills, NJ, USA) according to the same time schedule as SC hydration measurements. Based on a validated color scale, the hydration rate of each facial area was translated into colors (blue color = well hydrated; red color = dry). Then, the areas between the test sites were interpolated and the colors superimposed onto the digital facial images to create a continuous hydration map of the whole face.

Quantification of SC lipids involved in the barrier function of SC (i.e., ceramides, cholesterol, free fatty acids) was carried out as described previously [21]. Two skin surface samples (swab samplings) were collected at baseline and on days 7 and 28. One sample was taken on the right cheek and another one on the left cheek. Before sampling, the swabs were dipped in a buffered 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 [22].

To study the effects of DFC on skin elasticity, the Cutometer® MPA580 (Courage & Khazaka, Cologne, Germany) was used [21,23–26]. In our study, the parameters R2 (overall elasticity of the skin), R5 (net elasticity), and R7 (ratio of elastic recovery to the total deformation) were derived from the deformation by time curve [24]. The device software was used to generate the data. Single elasticity measurements were performed on the jawline at baseline and on day 28.

Prior to instrumental measurements (corneometry, skin elasticity), study participants remained in a climatized room (22 ± 2 °C, 45 ± 10% relative humidity) for 15 min to minimize the influence of environmental conditions on the measurement results.

To determine product satisfaction, the subjects had to complete a validated self-assessment questionnaire when they visited the study center on day 28. The questionnaire followed the guidance provided by the American Society for Testing and Materials [27]. For the assessment of product satisfaction, the subjects had to rate 49 statements about favorable traits and attributes on a numerical scale ranging from 0 to 6 (0 = strongly disagree, 1 = moderately disagree, 2 = slightly disagree, 3 = neither agree nor disagree, 4 = slightly agree, 5 = moderately agree, 6 = strongly agree). Moreover, at the end of the study, an acceptability scoring was completed by the technician (with the support of a dermatologist) and by the study participants using a numerical scale ranging from 0 to 3 (0 = bad acceptability, 1 = moderate acceptability, 2 = good acceptability, 3 = very good acceptability). During the entire study period, adverse events (AEs) were monitored.

2.1.4. Statistical Evaluation

The statistical evaluations were performed using Microsoft Excel® 2010 (Microsoft, Redmond, WA, USA) and SAS® 9.4 for Windows (IT@Cornell, Ithaca, NY, USA). For corneometry and skin elasticity measurements, a mixed analysis of variance (ANOVA) was conducted to test if there was a significant difference between baseline and subsequent measurements. The change from baseline was calculated based on adjusted means (least squares means (LS-means)) from ANOVA. For evaluation of skin capacitance/corneometry values, the mixed ANOVA model was fitted on the mean value of the 30 zones per subject. For statistical analysis of results from SC lipid content measurements, a mixed Friedman

ANOVA model was applied to identify significant mean changes from baseline. For all inferential analyses, the level of significance was set at 0.05. No adjustment for multiple testing was made. Results from the questionnaire, acceptability scoring, and AEs were evaluated descriptively.

2.2. Studies 2 and 3: DFC-SPF—Day Face Cream with SPF25 and NFC—Night Face Cream

The design, inclusion/exclusion criteria, and assessments of Studies 2 and 3 were identical to Study 1.

3. Results

3.1. Study 1: DFC—Day Face Cream

In total, 44 healthy subjects (15 Africans, 15 Asians, 14 Caucasians) were enrolled and 42 completed the study. Out of these, 36 were female and eight were male. The mean age was 34 years (range: 18–50 years). Two subjects were withdrawn from the study because they did not adhere to the study protocol.

3.1.1. SC Hydration (Corneometry)

Table 1 shows the skin capacitance/corneometry results for the face over the study course; mean absolute values (averaged over the 30 facial measurement sites) and mean changes from baseline (based on LS-means from ANOVA) are shown.

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

Time	Absolute Value	Change from BL *	*p*-Value #
BL	45.50 ± 7.41	-	-
24 h	50.24 ± 10.66	4.85 [2.58, 7.13]	0.0001
48 h	48.44 ± 9.48	2.74 [0.56, 4.93]	0.0151
Day 7	51.83 ± 10.89	6.35 [3.53, 9.17]	<0.0001
Day 14	52.85 ± 10.56	7.38 [4.90, 9.86]	<0.0001
Day 21	56.14 ± 11.50	10.66 [7.93, 13.40]	<0.0001
Day 28	57.61 ± 12.70	12.13 [8.90, 15.36]	<0.0001

N = 41–44. Data are given in arbitrary units (a.u.). The absolute values were assessed by corneometry and are presented as mean ± SD (at each time-point averaged over 30 facial measurement sites). Changes from baseline are presented as mean with 95% confidence interval. BL = baseline skin capacitance value before initial product application; h = hour. * Based on adjusted means (LS-means) from ANOVA. # For the mean change from baseline, as determined by the ANOVA model.

The single application of DFC and the following once-daily use induced an improvement in SC hydration, as reflected by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.05$ for all comparisons with baseline). After a single application, a skin-moisturizing effect was rapidly achieved (within 24 h), which was still apparent after 48 h. The improvement in the SC moisturization status became more pronounced as the study progressed. In all three ethnicities, the enhancement of SC hydration upon use of DFC was in the same range, resulting in an overall average increase from baseline by 26.6% on day 28 (12.13 a.u.; $p < 0.0001$), as shown in Table 1. Representative continuous capacitance color maps illustrating the improvement in skin hydration per ethnicity over the study course are shown in Figure 1.

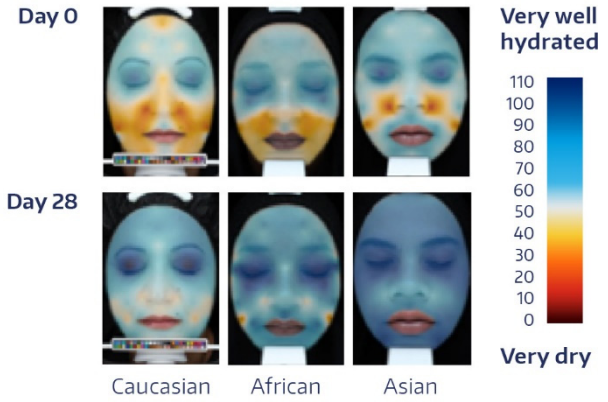

Figure 1. Continuous capacitance color maps of one representative subject per ethnicity. Color maps were assessed at baseline (Day 0) and following once-daily application of DFC over approximately 4 weeks (Day 28). The color code for corneometry values (0–110 a.u.) is shown on the right. Blue color represents hydrated skin and red color represents dry skin.

3.1.2. SC Lipid Content

Upon treatment of the face with DFC, there was a significant increase in mean ceramide levels by day 28 versus baseline in the whole study population (36.72 ± 22.31 vs. 29.89 ± 18.10 a.u./mg protein; 22.9% increase from baseline; $p = 0.0012$). The increase was apparent for all three ethnicities (Figure 2). The application of DFC had no significant effect on mean cholesterol (6.41 ± 3.02 vs. 5.79 ± 2.64 µg/mg protein; 10.7% increase from baseline; $p = 0.1210$) and mean free fatty acids levels (79.26 ± 56.41 vs. 70.43 ± 35.09 µg/mg protein; 12.5% increase from baseline; $p = 0.2822$) over the study period.

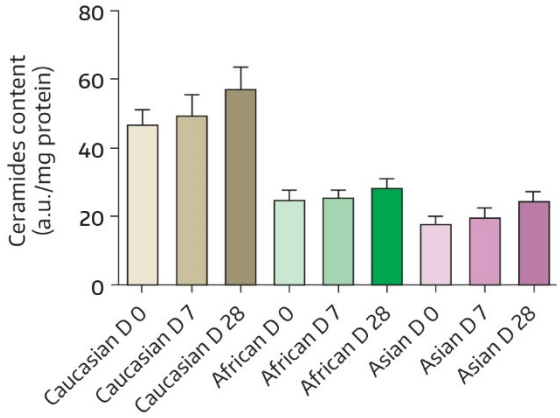

Figure 2. Mean ± SD content of ceramides in stratum corneum by ethnicity following once-daily application of DFC over approximately 4 weeks. N = 14, 14, and 14 for Caucasians, Africans, and Asians, respectively. D 0 = baseline value; D 7 = day 7; D 28 = day 28; a.u. = arbitrary units.

3.1.3. Skin Elasticity Parameters

Treatment of the face with DFC had no effects on skin elasticity parameters. R2, R5, and R7 parameters remained essentially unchanged over the study period (data not shown).

3.1.4. Self-Assessment Questionnaire, Acceptability, and Tolerability

The satisfaction with the cosmetic features of DFC was highly rated by study participants. Specifically, 47 of 49 statements related to product satisfaction were rated as 6 (strongly agree), 5 (moderately agree), or 4 (slightly agree) by ≥70% of subjects at the end of the study, suggesting that DFC performed favorably regarding pleasantness of use and appearance of the facial skin as well as DFC's capacity to moisturize, sooth, soften, and protect the facial skin. For instance, 91%, 82%, and 86% of subjects provided a score of

4–6 for the statements that DFC "leaves skin feeling moisturized", "leaves skin intensely hydrated", and "leaves skin feeling soft", respectively.

Likewise, the acceptability of DFC was highly rated by subjects and the technician. All subjects with available data (N = 42) scored the acceptability of DFC as good or very good, while the technician scored the acceptability as good or very good in 98% of evaluable subjects.

With regard to safety, applications of DFC were well tolerated. None of the subjects experienced a systemic AE. Two local AEs were considered product-related and of clinical relevance (two events of mild erythema on the cheekbones lasting for approximately 3 weeks).

3.2. Study 2: DFC-SPF—Day Face Cream with SPF25

Overall, 42 healthy subjects (14 of each ethnicity; 32 females, 10 males) were enrolled and all completed the study. The mean age was 41 years (range: 19–50 years).

3.2.1. SC Hydration (Corneometry)

Table 2 shows the skin capacitance/corneometry results for the face over the study course; mean absolute values (averaged over the 30 facial measurement sites) and mean changes from baseline (based on LS-means from ANOVA) are displayed.

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

Time	Absolute Value	Change from BL *	*p*-Value #
BL	47.77 ± 7.54	-	-
24 h	51.20 ± 10.94	3.42 [1.41, 5.43]	0.0014
48 h	51.89 ± 11.09	4.12 [2.01, 6.22]	0.0003
Day 7	56.00 ± 9.61	8.22 [6.28, 10.17]	<0.0001
Day 14	56.36 ± 10.33	8.59 [6.49, 10.69]	<0.0001
Day 21	58.71 ± 9.77	10.70 [8.69, 12.71]	<0.0001
Day 28	60.34 ± 8.49	12.57 [10.86, 14.28]	<0.0001

N = 39–42. Data are given in arbitrary units (a.u.). The absolute values were assessed by corneometry and are presented as mean ± SD (at each time-point averaged over 30 facial measurement sites). Changes from baseline are presented as mean with 95% confidence interval. BL = baseline skin capacitance value before initial product application; h = hour. * Based on adjusted means (LS-means) from ANOVA. # For the mean change from baseline, as determined by the ANOVA model.

The single application of DFC-SPF and the subsequent once-daily usage were associated with an improvement in SC hydration, as mirrored by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.05$ for all comparisons with baseline). After a single application, a skin-moisturizing effect was observed within 24 h, which was maintained until 48 h after the single treatment. Upon once-daily application, the SC moisturization status improved further. In all three ethnicities, there was a comparable improvement in SC hydration following DFC-SPF application, resulting in an overall average increase from baseline by 26.3% on day 28 (12.57 a.u.; $p < 0.0001$), as shown in Table 2. Selected continuous capacitance color maps illustrating the improvement in skin hydration per ethnicity during the study are shown in Figure 3.

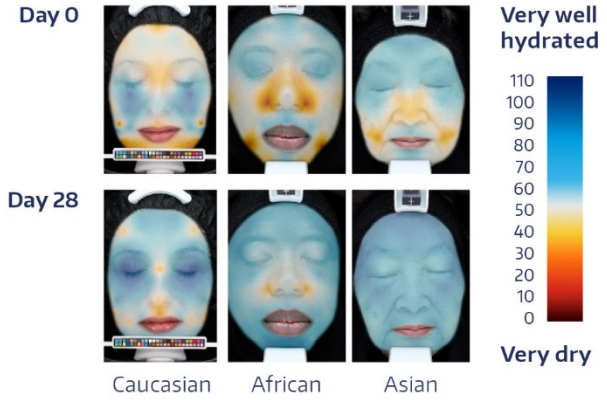

Figure 3. Continuous capacitance color maps of one representative subject per ethnicity. Color maps were assessed at baseline (Day 0) and following once-daily application of DFC-SPF over approximately 4 weeks (Day 28). The color code for corneometry values (0–110 a.u.) is shown on the right. Blue color represents hydrated skin and red color represents dry skin.

3.2.2. SC Lipid Content

Upon treatment of the face with DFC-SPF, there was a significant increase in mean cholesterol by day 28 versus baseline in the whole study population (9.20 ± 3.54 vs. 8.09 ± 3.46 µg/mg protein; 13.7% increase from baseline; $p = 0.0045$), whereas the application of DFC-SPF had no significant effect on mean free fatty acids levels (157.10 ± 67.87 vs. 144.70 ± 57.35 µg/mg protein; 8.6% increase from baseline; $p = 0.1181$). The change in mean cholesterol levels was more obvious in African and Caucasian subjects than in Asian subjects (Figure 4). The increase in mean ceramide content from baseline reached a statistical trend ($p < 0.1$) at the end of the study (34.12 ± 18.31 vs. 30.44 ± 16.72 a.u./mg protein; 12.1% increase from baseline; $p = 0.0844$).

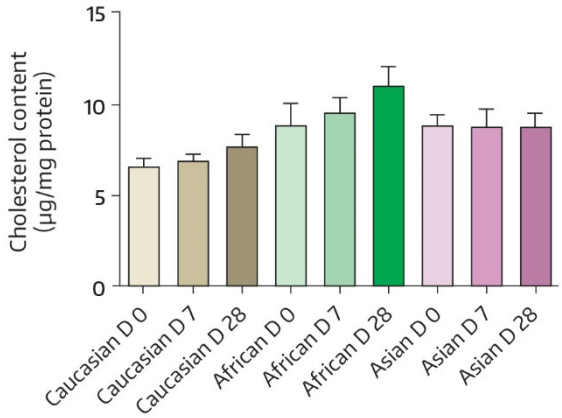

Figure 4. Mean ± SD content of cholesterol in stratum corneum by ethnicity following once-daily application of DFC-SPF over approximately 4 weeks. N = 14, 14, and 14 for Caucasians, Africans, and Asians, respectively. D 0 = baseline value; D 7 = day 7; D 28 = day 28.

3.2.3. Skin Elasticity Parameters

Treatment of the face with DFC-SPF had no effects on skin elasticity parameters. R2, R5, and R7 parameters remained unchanged over the study period (data not shown).

3.2.4. Self-Assessment Questionnaire, Acceptability, and Tolerability

The satisfaction with the cosmetic features of DFC-SPF was highly scored by study subjects. Specifically, 46 of 49 statements related to product satisfaction were rated as 6 (strongly agree), 5 (moderately agree), or 4 (slightly agree) by >70% of subjects at the end of the study, indicating that DFC-SPF performed favorably regarding pleasantness of use and appearance of the facial skin as well as DFC-SPF's capacity to moisturize, sooth,

soften, and protect the facial skin. For instance, 98%, 93%, and 95% of subjects provided a score of 4–6 for the statements that DFC-SPF "leaves skin feeling moisturized", "leaves skin intensely hydrated", and "leaves skin feeling soft", respectively.

Similarly, the acceptability of DFC-SPF was highly rated by subjects and the technician. The technician scored the acceptability of DFC-SPF as good or very good for all subjects; 98% of subjects rated the acceptability as good or very good.

The applications of DFC-SPF were well tolerated. None of the subjects experienced a systemic AE. In two subjects, local AEs were considered product-related and of clinical relevance (pimples of mild severity on the cheeks for approximately 2 weeks; prolonged mild erythema on the chin).

3.3. Study 3: NFC—Night Face Cream

In total, 42 healthy subjects (15 Africans, 13 Asians, 14 Caucasians) were enrolled, and all completed the study. Out of these, 34 were female and eight were male. The mean age was 37 years (range: 18–50 years).

3.3.1. SC Hydration (Corneometry)

Table 3 shows the skin capacitance/corneometry results for the face over the study course; mean absolute values (averaged over the 30 facial measurement sites) and mean changes from baseline (based on LS-means from ANOVA) are shown.

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

Time	Absolute Value	Change from BL *	*p*-Value #
BL	47.64 ± 5.67	-	-
24 h	53.33 ± 7.03	5.69 [3.46, 7.92]	<0.0001
48 h	53.95 ± 8.11	6.31 [3.97, 8.66]	<0.0001
Day 7	58.38 ± 7.40	10.74 [8.67, 12.81]	<0.0001
Day 14	58.00 ± 7.32	10.10 [7.47, 12.73]	<0.0001
Day 21	61.29 ± 6.93	13.65 [11.54, 15.75]	<0.0001
Day 28	60.30 ± 9.25	12.66 [9.92, 15.40]	<0.0001

N = 41–42. Data are given in arbitrary units (a.u.). The absolute values were assessed by corneometry and are presented as mean ± SD (at each time-point averaged over 30 facial measurement sites). Changes from baseline are presented as mean with 95% confidence interval. BL = baseline skin capacitance value before initial product application; h = hour. * Based on adjusted means (LS-means) from ANOVA. # For the mean change from baseline, as determined by the ANOVA model.

The single application of NFC and the following once-daily use triggered an improvement in SC hydration, recognizable by an enhanced electrical capacitance of the skin surface compared with baseline ($p < 0.0001$ for all comparisons with baseline). After single application, a skin-moisturizing effect was observed within 24 h, which was maintained until 48 h post single treatment. With continued once-daily NFC application, the SC moisturization became more pronounced, where approximately 80% of the maximum hydrating effect was already seen on day 7. In all three ethnicities, the enhancement of SC hydration upon use of NFC was in the same range, resulting in an overall average increase from baseline by 26.6% on day 28 (12.66 a.u.; $p < 0.0001$), as shown in Table 3. Representative continuous capacitance color maps showing the improvement in skin hydration per ethnicity over the study course are displayed in Figure 5.

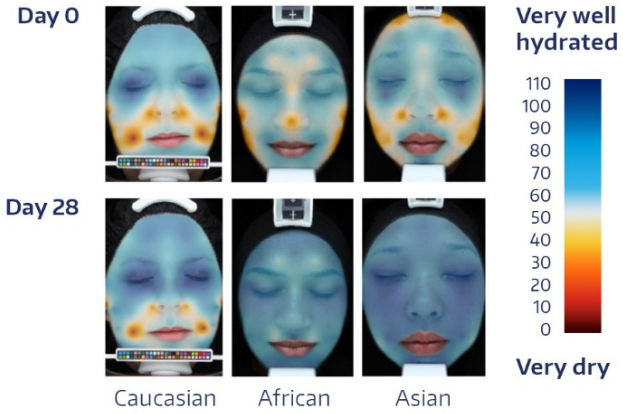

Figure 5. Continuous capacitance color maps of one representative subject per ethnicity. Color maps were assessed at baseline (Day 0) and following once-daily application of NFC over approximately 4 weeks (Day 28). The color code for corneometry values (0–110 a.u.) is shown on the right. Blue color represents hydrated skin and red color represents dry skin.

3.3.2. SC Lipid Content

Treatment of the face with NFC was associated with a significant increase in cholesterol, free fatty acids, and ceramide levels in the whole study population. By day 28, mean cholesterol content increased by 30.8% from baseline (10.10 ± 4.87 vs. 7.72 ± 2.67 µg/mg protein; $p < 0.0001$), mean free fatty acids levels increased by 42.4% (145.50 ± 83.99 vs. 102.20 ± 48.49 µg/mg protein; $p < 0.0001$), and mean ceramide content increased by 22.9% (25.37 ± 11.23 vs. 20.64 ± 11.78 a.u./mg protein; $p = 0.0028$). The increase in mean free fatty acids levels was observed in all three ethnicities (Figure 6), while the increases in mean cholesterol and mean ceramide contents were apparent only in African and Asian subjects.

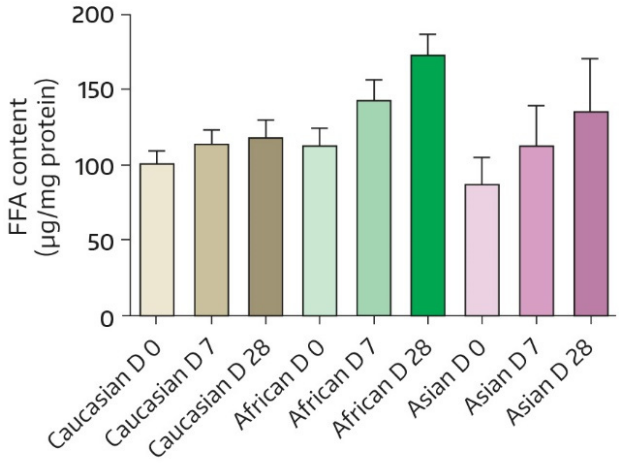

Figure 6. Mean ± SD content of free fatty acids in stratum corneum by ethnicity following once-daily application of NFC over approximately 4 weeks. N =14,15, and 13 for Caucasians, Africans, and Asians, respectively. D 0 = baseline value; D 7 = day 7; D 28 = day 28; FFA = free fatty acids.

3.3.3. Skin Elasticity Parameters

Treatment of the face with NFC had no effects on skin elasticity parameters. R2, R5, and R7 parameters remained essentially unchanged over the study period (data not shown).

3.3.4. Self-Assessment Questionnaire, Acceptability, and Tolerability

The satisfaction with the cosmetic features of NFC was highly scored by the study subjects. Specifically, 46 of 49 statements related to product satisfaction were rated as 6 (strongly agree), 5 (moderately agree), or 4 (slightly agree) by >70% of subjects at the end of the study, suggesting that NFC performed favorably regarding pleasantness of use and

appearance of the facial skin as well as NFC's capacity to moisturize, sooth, soften, and protect the facial skin. For instance, 98%, 98%, and 100% of subjects provided a score of 4–6 for the statements that NFC "leaves skin feeling moisturized", "leaves skin intensely hydrated", and "leaves skin feeling soft", respectively.

The acceptability of NFC was also highly rated by subjects and the technician. In total, 98% of subjects scored the acceptability of NFC as good or very good. Likewise, the technician scored the acceptability as good or very good in 98% of subjects.

In terms of safety, applications of NFC were well tolerated. None of the subjects experienced a systemic AE. Three local AEs were considered product-related and of clinical relevance (pimples of mild severity on different parts of the face for approximately 3 weeks, mild stinging in the perioral area for approximately 2 weeks, repeated occurrence of mild erythema on the nose).

4. Discussion

Three new dexpanthenol-containing face creams with different lipid contents (DFC, DFC-SPF, NFC) were developed for dry and sensitive skin sufferers. The objective of our trials was to investigate whether all of the new face creams are suitable for the daily face care (day and night) of dry/sensitive skin sufferers. For this purpose, three studies explored, for the first time, the effects of the new face creams on SC hydration, SC lipid content, and skin elasticity, as well as their acceptability (including product satisfaction and cutaneous tolerability) after single and prolonged once-daily application in three ethnic groups with dry and sensitive skin.

If compared with baseline assessments, the study results can be summarized as follows: (1) following a single application of DFC, DFC-SPF, and NFC to dry skin of the face, skin capacitance was significantly increased for up to 48 h, indicating long-lasting skin hydration; (2) following once-daily application of DFC, DFC-SPF, and NFC to facial dry skin for approximately 4 weeks, skin capacitance was significantly increased at all assessment time-points, indicating long-term hydration; (3) the favorable effects of DFC, DFC-SPF, and NFC on the facial moisturization status were observed in all three ethnic groups; (4) the enhancements in SC hydration were not paralleled by improvements in skin elasticity parameters; (5) the once-daily usage of DFC, DFC-SPF, and NFC was associated with a significant increase in cholesterol, free fatty acid, and/or ceramide levels in the SC; (6) the pattern of lipid changes was not consistent among the face creams tested and between ethnic groups; (7) all three face creams were well tolerated and achieved a high product satisfaction and acceptability by study participants; (8) all three face creams are suitable for the daily face care (day and night) of dry skin sufferers with different ethnic backgrounds (African, Asian, Caucasian).

The face creams showed a good performance in dry skin sufferers of different ethnicity. In particular, they were all effective facial skin moisturizers as required for state-of-the-art face creams. In addition, lipids necessary for skin barrier function were replenished. The observed SC hydrating effects were in agreement with previous trials using emollients with a similar composition [16,21]. Considering recent research, it may be inferred that the favorable effects on skin hydration mediated by DFC, DFC-SPF, and NFC are triggered by their key ingredients which likely act in a synergistic/additive fashion. As a physiological humectant of small size, glycerin plays a major role in the moisturization of the SC. After topical application, it reaches the deeper cell layers of the SC, where it binds water in the interlamellar spaces and mimics the function of natural moisturizing factors [1,11,28]. Dexpanthenol has diverse properties. Due to its hygroscopic features, it promotes retention of moisture. It also compensates for reduced hydration by retaining/increasing molecular mobility/fluidity of the SC lipid lamellae and proteins. Dexpanthenol is able to generate properties of hydrated skin also in dehydrated conditions [29]. In addition to its actions as a humectant, dexpanthenol stimulates intracellular protein and lipid synthesis, increases fibroblast proliferation, and enhances epidermal differentiation [1,14]. Dry skin reveals a decreased lipid content. The nonphysiological and physiological lipids present in DFC,

DFC-SPF, and NFC act as replacements for lost natural skin lipids in dry skin conditions and improve the water-binding capacity of the SC [16,21]. The non-physiological lipids (argan oil, shea butter, squalane) present in the new face creams largely stay on the SC surface, where they provide hydrating effects by working as an occlusive dressing [1]. The physiological lipid (isopropyl isostearate) penetrates the SC and increases the hydration level by supporting normalization of the affected lipid organization/composition [1,30]. These favorable effects of lipids on SC hydration may explain why NFC, having the highest lipid content, showed the fastest skin-moisturizing effect among the three face creams tested (approximately 80% of maximum effect within 1 week).

For none of the face creams studied, the enhancement in SC hydration was accompanied by increases in skin elasticity parameters. This appears in contradiction with previous investigations suggesting that enhanced SC hydration is associated with improvements in the biomechanical properties of the skin (forearm) [21,31]. However, it needs emphasis that in our study, we integrated skin capacitance results from 30 facial sites to account for local variations in skin hydration, while skin elasticity parameters were assessed as single measurements on selected spots on the jawline only. Skin areas on the jawline might be less reactive to exogenous hydration than other regions of the facial skin, thus explaining why skin hydration results integrated over half of the face did not correlate with skin elasticity parameters. In fact, previous attempts failed to establish a mutual relationship between skin hydration results integrated over the face and elasticity parameters measured on different single spots on the face [32].

Ceramides, together with cholesterol and free fatty acids, form the intercellular lipid matrix of the SC. These lipids are required for adequate SC hydration and are major contributors to SC barrier function [33,34]. In our studies, we observed a significant increase in SC cholesterol, SC free fatty acid, and/or SC ceramides upon prolonged use of DFC, DFC-SPF, and NFC. This finding can be attributed to niacinamide, which is an ingredient of DFC, DFC-SPF, and NFC. Niacinamide, an amide of vitamin B_3, penetrates the SC effectively and increases the biosynthesis of natural SC lipids [12,13,35], apart from its antipruritic/soothing properties [13]. The effect of niacinamide on natural SC lipid content may have contributed to the increased facial moisturization mediated by DFC, DFC-SPF, and NFC. Our results are in accordance with previous healthy subject studies using niacinamide-containing emollients [16,21]. In those 4-week trials, the topical study products caused a significant increase in mean SC cholesterol and mean SC free fatty acids levels in dry skin sufferers. Moreover, topical dexpanthenol stimulates lipid synthesis in the SC, thereby contributing to the replenishment of lost SC lipids in dry skin conditions [14]. Finally, the observed enhanced lipid synthesis could be the consequence of improved SC hydration. Previous works showed that better SC hydration increases the activity of enzymes [1,36]. Hence, the improvement in SC moisturization might increase the activity of enzymes related to epidermal lipid synthesis and/or activation of lipid precursors [37]. Among the new face creams tested, NFC had the most pronounced and consistent effect across all three lipids evaluated. This may have been a secondary effect of NFC's fast SC hydrating properties inducing an expedited increment in the activity of enzymes. However, the exact reason why the pattern of lipid changes was not consistent among the face creams tested and between ethnic groups remains to be elucidated.

Despite enrolling subjects with sensitive skin, DFC, DFC-SPF, and NFC were well tolerated in our trials and achieved a high product satisfaction and acceptability by study participants. This is in agreement with previous trials using emollients with a similar composition [16,21].

Our studies have limitations. Due to the absence of control facial skin areas for quantification of SC hydration and SC lipids, we were not able to detect spontaneous changes in these parameters over the 4-week study periods. In addition, given the lack of active comparators, no superiority claims over other face creams can be made. Finally, the effects of DFC, DFC-SPF, and NFC on TEWL as a measure of skin barrier function were not measured in our studies. This will be the subject of separate trials.

5. Conclusions

The results of our trials indicate that all three face creams studied are suitable for the daily face care (day and night) of dry skin sufferers with different ethnic backgrounds (African, Asian, Caucasian). Their single and prolonged once-daily usage was associated with significant SC-hydrating effects. Favorable effects of DFC, DFC-SPF, and NFC on facial moisturization were observed in all three ethnic groups. Results from lipid analyses suggested that the prolonged application of DFC, DFC-SPF, and NFC supports the replenishment of lost lipids in the outer layers of the SC. All three face creams were well tolerated by study participants in our 4-week studies and experienced a high product satisfaction and acceptability. Hence, DFC, DFC-SPF, and NFC may become a valuable addition to the range of topical skin care products needed for the daily care of dry and sensitive facial skin, satisfying consumers of different ethnicities.

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Institutional Review Board Statement: The studies were conducted in accordance with the Declaration of Helsinki with all its amendments, Good Clinical Practice, and local regulatory requirements. Ethical review and approval were waived for these cosmetic studies for the following reason: study centers were located in France and Mauritius. According to the French public health law, studies investigating cosmetic products do not require ethical review and approval because they evaluate the ability of a product to cleanse, perfume, modify the appearance, protect, maintain the human body in good condition, or to correct body odor. For Mauritius, according to the Clinical act 2011 review by the Clinical Research Regulatory Council (national body), ethics committee review is mandatory only for medical devices and pharmaceutical products. Products falling under the cosmetic definition are not reviewed. The participants were warned of the risks involved before they agreed to participate in this study.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the studies. Written informed consent has been obtained from the subjects to publish photographs of their faces in this paper.

Data Availability Statement: The data presented in this paper are available from the corresponding author upon reasonable request.

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Conflicts of Interest: S.T., R.d.S. and H.S. are employees of Bayer Consumer Care AG, Basel, Switzerland. A.B.-G. is an employee of Bayer Hispania, S.L., Sant Joan Despí, Spain. The other authors report no conflict of interest.

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