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A new topical panthenol-containing emollient: skin-moisturizing effect following single and prolonged usage in healthy adults, and tolerability in healthy infants

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ABSTRACT

Purpose: Two studies were conducted with a new topical panthenol-containing emollient (NTP-CE) to investigate the skin-moisturizing effect in healthy adults and tolerability in healthy infants.

Methods: In Study 1 ($N = 44$), a single skin application of NTP-CE was performed followed by a 4-week twice-daily application. Skin hydration and stratum corneum (SC) water content change (using Raman spectroscopy) were measured. In the 4-week Study 2 ($N = 65$, aged 3–25 months), NTP-CE tolerability was assessed using a 5-point scoring system; skin hydration was determined in a subset ($N = 21$).

Results: In Study 1, mean $AUC_{0-24\,h}$ for skin capacitance change from baseline was 302.03 i.u. with NTP-CE and −15.90 i.u. in control areas ($p < .001$). With NTP-CE (at 4 h), the water content within the upper SC part was reduced (−45.10 vs. −13.39 g/cm^2, $p = .013$) and the water gradient increased (0.51 vs. 0.11 g/cm^4, $p = .036$), indicating relocation of water into deeper layers. In Study 2, there was no statistically significant change from baseline in mean cutaneous tolerability scores. At days 7, 14, and 28, skin hydration had increased by 42%, 54%, and 49%, respectively (all $p < .001$).

Conclusions: Single and prolonged NTP-CE usage is associated with sustained and deep skin moisturization. NTP-CE is well tolerated by healthy infants.

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Introduction

A new topical panthenol-containing emollient (NTP-CE, Bepanthen® SensiDaily) has been developed for subjects with non-inflammatory dry and sensitive skin conditions, such as atopic dermatitis (AD) while in remission phase between two flares (1). In fact, recent studies showed that the use of emollients can prolong the time between AD flares (2). NTP-CE is a water-in-oil emulsion formulation to be used as cosmetic product for daily care. The key ingredients are panthenol, glycerin, different lipids (e.g. ceramide 3), vitamin B_3, and α-glucan oligosaccharide. In addition, NTP-CE incorporates a lipid lamellar technology resembling naturally occurring skin barrier lipids. To become a useful adjunct in the management of AD and other conditions associated with dry skin, NTP-CE has to provide skin-moisturizing potential (3). Findings of an initial set of two studies in healthy adult subjects suggested that twice-daily application of NTP-CE is well tolerated and associated with significant improvements in skin barrier restoration, skin moisturization, and intercellular lipid layer (ICLL) organization in the stratum corneum (SC). In addition, there was some indication that NTP-CE exerts favorable effects on the skin microflora by supporting the growth of commensal bacteria (4). However, the duration of skin moisturization and its maintenance upon long-term NTP-CE use was not investigated. Moreover, no information was obtained on the influence on water distribution within the skin barrier following NTP-CE use. Finally, the trials did not include children. As AD often manifests in infancy (5), a satisfactory local tolerability of NTP-CE has to be assured in the vulnerable population of infants. It has been estimated that the onset of AD occurs during the first 12 months of life in 60% of affected subjects (6). Also outside the AD setting, there may be a rationale for the use of emollients in infants (e.g. to prevent the occurrence of diaper rash) (7).

It was expected that NTP-CE has long-lasting and sustained skin-moisturizing potential, and is well tolerated by small children. As not all emollients/moisturizers perform identically (8,9) and claims for cosmetic products have to be supported by adequate and verifiable evidence (10), the two studies presented here were conducted to investigate the skin-moisturizing effect of NTP-CE in healthy adults (Study 1) and to assess its tolerability in healthy infants (Study 2). The randomized controlled Study 1 explored skin hydration after a defined single application of NTP-CE over a period of 24 h and after prolonged usage over 4 weeks in healthy adult subjects with dry skin. Furthermore, the change in water distribution within SC was assessed using confocal *in vivo* Raman spectroscopy. The non-comparative Study 2 investigated the cutaneous tolerability of NTP-CE and its impact on skin hydration in healthy infants when applied twice-daily on face and body for 4 weeks.

Methods

Study 1: moisturization study

The trial was conducted in healthy adult subjects at *proDERM* Institute for Applied Dermatological Research, Schenefeld/Hamburg,

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Germany between November and December 2014. The study was performed according to the principal requirements of the Declaration of Helsinki with all its amendments. Subjects gave written informed consent to participate after being informed about the study. The new cosmetic emollient Bepanthen® SensiDaily (Bayer Consumer Care AG, Basel, Switzerland) was used in the trial. Ethics approval was obtained from an independent German Ethics Committee.

Given the exploratory nature of the study, no formal sample size calculation was performed. For the same reason, no primary and secondary variables were defined. Based on historical data, it was expected that scientifically meaningful results can be obtained with the selected sample size (11–14).

Study design

This was an open-label, randomized, intra-individual comparison study in healthy adult subjects with dry skin. One skin site (6 cm ×12 cm) was selected and marked on each volar forearm (i.e. two test areas in total). NTP-CE was always applied on the same skin area of one volar forearm. The area of the contralateral arm remained untreated and served as negative control. For each application, a pea-size amount of NTP-CE (approximately 2 mg/cm^2) was to be applied on the assigned test area. Compliance was assured by weighing each bottle with NTP-CE before and after the use period. The allocation of treatment (NTP-CE use versus untreated) to the two skin areas was done according to a balanced randomization list generated by a data manager prior to study start.

Study visits took place at screening, baseline (day 1) as well as on study days 2 and 29. On day 1, a single application of NTP-CE was performed by a technician. On day 2, 24 h after the first application, twice-daily application (morning and evening) by the subjects themselves commenced and was continued until day 28. On day 29, the subjects returned to the study site without having applied NTP-CE in the morning. There was no overnight confinement of study subjects.

Subjects and assessments

In total, 44 healthy male and female subjects between 18 and 65 years of age with white skin (type I–III on Fitzpatrick scale (15)) were to be enrolled. At screening, they had to have dry skin on the volar forearms corresponding to a corneometry value of less than 40 instrumental units (i.u.). Subjects were not allowed to use other topical preparations on the test areas within 7 days prior to and during the study. Similarly, intensive exposure of test areas to ultraviolet light was not permitted within 3 days before and throughout the trial. On days of instrumental measurements, the use of detergents was not allowed on test areas, neither was the application of water within 2 h before assessments. For inclusion, females had to be non-pregnant and non-breastfeeding. Female subjects of childbearing age were required to use reliable methods of contraception during the study. Subjects were excluded if they had an active skin disease, dark pigmentation or non-uniform skin color at the test areas, allergies to any ingredient of NTP-CE, any condition at the test areas influencing assessments (e.g. moles, tattoos, scars, irritated skin, hair), or took any antiphlogistic/analgesic medication (except for low doses of acetylsalicylic acid or paracetamol) within the last 3 days before study start.

Skin hydration was determined by corneometry (Corneometer® CM825, Courage & Khazaka, Cologne, Germany) which measures the electrical capacitance of the skin. Capacitance is considered a function of SC hydration (16). Measurements were performed on each of the two test areas at baseline as well as at 2, 4, 8, and 24 h after the first and single application of NTP-CE. Another assessment took place on day 29 (i.e. after cessation of the twice-daily application period on day 28). There were five measurements per test area per assessment time. Values less than 30 i.u. represent very dry skin, 30–40 i.u. reflect dry skin, and values ≥40 i.u. are typically associated with normal skin. Thus, an increase in corneometry values mirrors a skin-moisturizing effect (17).

In a subset of 10 subjects (all body mass index ≤30), confocal Raman spectroscopy was to be conducted on each of the two test areas at baseline as well as at 4 and 8 h after the first application of NTP-CE. Raman spectroscopy, an established noninvasive method (18,19), was used to evaluate the change in water distribution within the SC after a single application of NTP-CE. Approximately 10 water profile measurements were performed in the center of each test area per assessment time as described before (20,21), thereby investigating the skin down to a depth of about 30 μm. The SC was divided into three equally spaced compartments (22), and the change in water content within each SC compartment was calculated according to the area under the curve (AUC) (20). In addition, the water gradient (slope of water increase) from outer to inner SC and SC thickness were calculated (20,21).

Before instrumental measurements (corneometry and confocal Raman spectroscopy), subjects remained in a climatized room (21 ± 1 °C, 50 ± 5% relative humidity) for at least 30 min. Adverse event (AE) monitoring took place over the entire study course.

Statistical evaluation

All statistical analyses were performed using SAS 9.3 for Windows. The full analysis set (FAS; all enrolled subjects with at least one post-application assessment) and safety population (all enrolled subjects who received at least one application of NTP-CE) were analyzed. The robustness of these results was to be investigated by comparison with per protocol (PP) analysis results. Changes from baseline were calculated. In addition, for changes from baseline in skin capacitance and water content within each SC compartment (after a single NTP-CE application), the AUC over 24 h and 4 and 8 h, respectively, was calculated as a summary measure for each subject using the cumulative trapezoidal rule (23). Bilateral differences between NTP-CE-treated and non-treated areas, in terms of change from baseline, were statistically analyzed using the paired *t*-test at the significance level of 0.05. No adjustment for multiple testing was made. AEs were evaluated descriptively.

Study 2: tolerability study in healthy infants

This trial was conducted in healthy infants at Dermscan Poland, Gdansk, Poland between January and June 2015. The study protocol was reviewed and approved by an independent Polish Ethics Committee, and written informed consent was obtained from the parents or legal guardians of the children before enrollment. The new cosmetic emollient Bepanthen® SensiDaily (Bayer Consumer Care AG, Basel, Switzerland) was used in the trial.

No formal sample size calculation was performed. However, considering other pediatric studies, it was expected that local tolerability of NTP-CE can be assessed with the selected sample size (24–26). The primary study objective was to assess the cutaneous tolerability of NTP-CE when applied twice-daily on face and body for 4 weeks. Secondary objective was evaluation of the moisturizing effect of NTP-CE after 7, 14, and 28 days of use as measured by corneometry.

Study design

This was an open-label, non-comparative study in healthy infants and involved four visits to the investigating center: on day 0 (screening and baseline) and study days 7, 14, and 28. NTP-CE was applied (gentle massaging onto clean skin) twice-daily by the parents on the infants' whole body and face for 4 weeks. NTP-CE usage replaced the skin care products the infants were already receiving on face and body (face cream, body balm, or lotion). Study visits took place without having applied NTP-CE in the morning. There was no overnight confinement of study subjects/parents. Compliance was checked by means of a diary the parents had to complete in terms of number of applications.

Subjects and assessments

Healthy male and female infants between 3 and 24 months of age with non-sensitive white skin (type I–III on Fitzpatrick scale (15)) were to be enrolled. Infants with dry skin were also permitted to participate. Dry skin was defined as a corneometry value of less than 35 i.u. on the forearms. It was planned to have at least 50 subjects evaluable for cutaneous tolerability following NTP-CE usage for 4 weeks. Parents were instructed not to change the usual hygienic care of the infants. Excessive exposure of the infants to ultraviolet light was not permitted within 30 days before and throughout the trial. Subjects were excluded if they had an active skin disease on face or body, allergies to any ingredient of NTP-CE, a condition requiring topical or systemic treatment interfering with tolerability assessments within 30 days before the study, or vaccination within 2 weeks prior to or scheduled vaccination during the trial.

Evaluation of cutaneous tolerability was performed by a pediatrician before first NTP-CE application (day 0) and on study days 7, 14, and 28. The skin of face and body was investigated for the presence of erythema, edema, dryness, desquamation, roughness, and vesicles. Each item was graded on a 5-point scale (0–4), with a score of 0 (not present) denoting the best condition and 4 (severe) the worst. The parents recorded reactions of their infants to NTP-CE daily in a diary which specified the following parameters: anxiety/crying, scratching, warm sensation, erythema, and sleeping quality. Each item was graded on a 5-point scale (0–4) as for clinical scoring. In addition, any other observation/AE had to be documented in the diary.

In a subset of subjects with dry skin, skin hydration was determined by corneometry (Corneometer® CM825, Courage & Khazaka, Cologne, Germany). Measurements of electrical capacitance of the skin were performed on pre-defined areas of forearms at baseline and on days 7, 14, and 28, after subjects had remained in a climatized room for approximately 30 min.

Statistical evaluation

All statistical analyses were performed using SPSS (version 22, IBM, Armonk, NY). For all parameters and measurement times, changes from baseline were calculated and evaluated descriptively. Mean changes from baseline related to tolerability scores and skin hydration were statistically analyzed using the paired *t*-test at a significance level of 0.05.

Results

Study 1: moisturization study

In total, 44 healthy subjects (32 females, 12 males) were enrolled and all completed the study. The mean age ± standard deviation (SD) was 45.9 ± 15.3 years; all subjects were included in the FAS. No PP analysis was performed because the number of subjects in the FAS and PP population was identical.

Table 1. Change from baseline of skin moisture measurements following single application of NTP-CE (first 24 h) and after twice-daily topical application over 4 weeks (day 29).

–	A	B	*p* Values[a]
Baseline	33.61 ± 5.07	32.90 ± 4.63	–
2 h	0.43 ± 3.23	21.88 ± 7.31	<.001
4 h	0.76 ± 2.79	22.23 ± 5.96	<.001
8 h	−0.48 ± 2.93	18.34 ± 6.69	<.001
24 h	−1.72 ± 3.62	3.76 ± 3.49	<.001
AUC_{0-24h}	−15.90 ± 49.03	302.03 ± 97.32	<.001
Day 29[b]	−2.46 ± 4.93	5.58 ± 7.36	<.001

$N = 44$. Data are given in i.u. All values are presented as mean ± SD.
A: untreated area; B: treated with NTP-CE; Baseline: baseline corneometry value before product application; 2 h/4 h/8 h/24 h: change from baseline by hours after product application; AUC_{0-24h}: area under the curve from baseline over 24 h after single application of NTP-CE; h: hour; Day 29: change from baseline after 4 weeks of application.
[a]For mean change from baseline (B vs. A), paired *t*-test.
[b]Measurement took place approximately 12–16 h after last NTP-CE application.
Note: An increase in skin capacitance reflects a skin-moisturizing effect.

SC hydration (corneometry)

Table 1 represents the corneometry results gathered during the study in terms of changes from baseline. At baseline, the two skin areas designated to be treated or untreated had similar mean values for dryness corresponding to dry skin. The single application of NTP-CE produced an increase in SC hydration as reflected by an enhanced electrical capacitance of the skin surface compared with baseline, whereas in the untreated control area electrical capacitance remained essentially unchanged. The skin-moisturizing effect was most pronounced at the early assessments but was still apparent after 24 h ($p < .001$ for all comparisons with control). Similarly, mean AUC for skin capacitance change from baseline over the initial 24-h measurement period was significantly greater when compared with the untreated area on the contralateral volar forearm ($p < .001$). After prolonged twice-daily NTP-CE usage over 4 weeks the skin capacitance change from baseline was again significantly greater compared with control. The results indicate that single and prolonged usage of NTP-CE is associated with skin-moisturizing effects.

Water distribution within SC (Raman spectroscopy)

For the skin area treated with NTP-CE, a statistical trend ($p < .1$) toward a higher water content (in terms of AUC change from baseline) was observed for the deepest SC compartment (Part 3) compared with untreated control at both assessment time points (Table 2). Based on treatment differences to baseline, this was accompanied by a significantly lower water content in the upper SC compartment (Part 1) and a significantly increased water gradient within the SC (both at 4 h) as well as a strong trend toward increased SC thickness following application of NTP-CE at both assessment time points (Table 2).

Overall, the confocal Raman spectroscopy results suggest that NTP-CE application induces a relocation of the water molecules into deeper layers of the SC which is associated with SC thickening.

Tolerability

On day 29, the day after last NTP-CE application, one subject reported local AEs (erythema, itching, and papules) of mild severity at the site NTP-CE was applied. Subsequently, the conditions recovered. Two subjects reported AEs (diarrhea, common cold)

Table 2. Results of Raman spectroscopy assessments related to SC at baseline and change from baseline following single application of NTP-CE.

					p Values[a]	
Parameter	–	Baseline	4 h	8 h	at 4 h	at 8 h
AUC (Part 1) [g/cm^2]	A	196.15 ± 35.76	−13.39 ± 20.81	−20.78 ± 29.32	.013	.537
	B	183.60 ± 17.12	−45.10 ± 30.46	−28.19 ± 29.73	–	–
AUC (Part 2) [g/cm^2]	A	283.21 ± 40.26	−20.05 ± 29.45	−28.87 ± 41.63	.981	.230
	B	263.49 ± 23.34	−20.35 ± 44.75	−8.26 ± 56.16	–	–
AUC (Part 3) [g/cm^2]	A	367.95 ± 46.65	−26.80 ± 41.37	−37.03 ± 55.61	.086	.061
	B	340.94 ± 30.41	3.82 ± 61.97	11.44 ± 87.08	–	–
Water gradient [g/cm^4]	A	2.09 ± 0.33	0.11 ± 0.19	0.14 ± 0.21	.036	.249
	B	2.22 ± 0.18	0.51 ± 0.41	0.31 ± 0.37	–	–
Thickness [μm]	A	19.57 ± 2.41	−1.31 ± 1.77	−1.64 ± 2.59	.057	.059
	B	18.04 ± 1.54	0.64 ± 3.18	0.94 ± 4.68	–	–

$N = 10$. All values are presented as mean ± SD.
A: untreated area; B: treated with NTP-CE; Part 1: upper SC compartment; Part 2: intermediate SC compartment; Part 3: deep SC compartment; Baseline: baseline value before product application; 4 h/8 h: change from baseline by hours after product application.
[a]For change from baseline (B vs. A), paired *t*-test.

Table 3. Change from baseline in cutaneous scores for dryness and roughness during twice-daily topical application of NTP-CE over 4 weeks in infants.

Dryness	*Body*	*Face*
Baseline ($N = 57$)	0.4 ± 0.1	0.4 ± 0.1
Day 7 ($N = 56$)	−0.3 ± 0.1 [−65%]	−0.2 ± 0.1 [−56%]
Day 14 ($N = 55$)	−0.4 ± 0.1 [−87%]	−0.3 ± 0.1 [−76%]
Day 28 ($N = 52$)	−0.4 ± 0.1 [−88%]	−0.1 ± 0.1 [−38%]
Roughness	*Body*	*Face*
Baseline ($N = 57$)	0.2 ± 0.1	0.2 ± 0.1
Day 7 ($N = 56$)	−0.2 ± 0.1 [−92%]	−0.1 ± 0.1 [−59%]
Day 14 ($N = 55$)	−0.2 ± 0.1 [−93%]	−0.2 ± 0.1 [−76%]
Day 28 ($N = 52$)	−0.1 ± 0.1 [−44%]	0.0 ± 0.1 [9%]

Values are presented as mean ± SEM [% change from baseline].
Baseline: baseline value before product application; Day 7/Day 14/Day 28: change from baseline by days after initiation of product application.
Note: Worst possible rating = 4. A decrease in scores reflects improved condition.

unrelated to NTP-CE treatment. Otherwise, no AE or serious AE was recorded.

Study 2: tolerability study in healthy infants

A total of 65 healthy infants (36 girls, 29 boys) between 3 and 25 months of age (mean: 11.6 months) were enrolled, among them 23 subjects with dry skin. Most subjects ($N = 52$, 80%) completed the 28-day study according to protocol. The reasons for subjects dropping out of the trial were loss to follow-up ($N = 9$) and non-adherence to the study protocol ($N = 4$).

Tolerability

NTP-CE applications were well tolerated. None of the infants experienced a systemic AE considered to be NTP-CE-related by the investigator. In two subjects, mild to moderate local erythema, papules and/or itching was observed. There was no statistically significant change from baseline in mean cutaneous tolerability scores for any item. For the items erythema, edema, desquamation and vesicles, average scores remained virtually unchanged over the study course with a baseline score of mostly 0 at both face and body (data not shown). The scores related to dryness and roughness decreased numerically during the study at almost all assessments (Table 3), most likely due to a better skin hydration. This applied on both face and body.

In accordance with the favorable tolerability of NTP-CE, the parents' scores related to anxiety/crying, scratching, warm sensation, erythema, and sleeping quality remained all unchanged during the study (data not shown).

Table 4. Change from baseline in skin capacitance during twice-daily topical application of NTP-CE over 4 weeks in infants with dry skin.

–	Corneometry result	*p* Values[a]
Baseline ($N = 21$)	28.38 ± 4.25	–
Day 7 ($N = 20$)	12.15 ± 9.39	<.001
Day 14 ($N = 21$)	15.24 ± 8.84	<.001
Day 28 ($N = 17$)	14.00 ± 7.43	<.001

Data are given in i.u. All values are presented as mean ± SD.
Baseline: baseline corneometry value before product application; Day 7/Day 14/Day 28: change from baseline by days after initiation of product application.
[a]For mean change from baseline, paired *t*-test.
Note: The observed increases in skin capacitance reflect a skin-moisturizing effect.

SC hydration (corneometry)

In 17–21 infants with dry skin, skin hydration was determined over the study course. Table 4 represents the corneometry results assessed in these subjects during the study in terms of changes from baseline. The 4 weeks' use of NTP-CE produced a sustained increase in SC hydration as reflected by a significantly enhanced electrical capacitance of the skin surface compared with baseline. After day 7, there was only a small additional increase in SC hydration suggesting that maximum moisturizing effects were achieved within 1 week of treatment. Specifically, at days 7, 14, and 28, skin hydration had increased by 42%, 54%, and 49%, respectively.

Discussion

In the context of the development of NTP-CE, one study explored the skin-moisturizing effect following single and prolonged usage as well as the change in SC water distribution in healthy adults with dry skin. Another study investigated the cutaneous tolerability of NTP-CE in healthy infants.

The findings of these two studies can be summarized as follows: (1) after a single application of NTP-CE, skin capacitance was significantly higher than on untreated skin for up to 24 h indicating long-lasting moisturization; (2) following twice-daily application of NTP-CE for 4 weeks, skin capacitance was significantly higher compared with untreated skin suggesting long-term moisturization; (3) after a single application of NTP-CE, the water content within the upper part of the SC was significantly reduced and the water gradient significantly increased for up to 4 h in comparison with control, indicating a relocation of the water molecules into deeper layers of the SC; (4) NTP-CE-induced deep moisturization as indicated by a trend toward increased water content in

the deepest SC compartment in association with increased SC thickness for up to 8 h compared with untreated skin; and (5) twice-daily NTP-CE use in healthy infants for 4 weeks was associated with favorable local tolerability and long-term moisturizing effects.

In healthy human skin, the intercellular lipid matrix shows a unique lamellar arrangement in the SC and consists mainly of ceramides, cholesterol and free fatty acids (27,28). SC lipids are necessary for proper SC hydration and dry skin is typically lipid-depleted (6,29,30). Recently, it was shown that NTP-CE application on dry skin induces a structural change of lipid arrangement within the SC which is associated with an increased ceramide 3, cholesterol and free fatty acids content, and an increased length of intercellular lipid lamellae (4). Hence, it may be inferred that the mechanisms by which NTP-CE exerts short- and long-term skin moisturization involves SC replenishment with lipids and restoration of intercellular lamellar lipid structures. Consequently, the innate water-binding capacity of the SC is generally improved. In addition, hydrophobic lipid components of NTP-CE (e.g. ceramide 3) may displace water molecules from the upper to deeper parts of the SC yielding an increased water gradient and thus deep moisturization. This hypothesis is supported by previous experimental studies and trials in which individual key components of NTP-CE have been investigated.

The topical application of SC lipids to a lipid-depleted SC sample caused a significant recovery of bound-water content to almost normal levels which was associated with restoration of the lamellar structure between the SC cells as assessed by ultrastructural analysis. It was suggested that SC lipids serve a water-holding function through the formation of lamellar structures within the SC (31). In a blinded randomized 3-week study in healthy subjects, the application of a vitamin B_3 (nicotinamide)-containing moisturizer to the volar forearm, increased SC thickness, water gradients and hydration as measured by confocal Raman spectroscopy (13). The SC swells as the water content increases leading to SC thickening (32). An increase in SC thickness upon topical application has also been reported for a lipophilic niacin derivative (33). Vitamin B_3 is known to increase biosynthesis of ceramides as well as other natural SC lipids (34,35).

Glycerin-based creams increased the water concentration compared with baseline at skin depths of 0–20 μm in healthy subjects as measured by a confocal Raman microprobe technique (19,36). Moreover, the repeated application (twice-daily for 10 days) of a 20% glycerin-containing cream resulted in a significant increase in SC hydration compared with placebo in a double-blind study in healthy volunteers (37). Ultrastructural studies indicated that glycerin binds water in the interlamellar spaces of the SC (38).

For a topical panthenol-containing cream (70% lipids, 5% panthenol), it has been reported to enhance SC hydration when applied twice-daily for seven days (39). In another study, topical panthenol formulated in two different lipophilic vehicles was applied on the skin of healthy subjects. Twice-daily application over seven days significantly improved SC hydration compared with controls (11). In a randomized, intra-individual comparison in AD patients, topical application of a moisturizer containing a ceramide precursor resulted in significantly increased skin hydration in the treated skin area compared with untreated skin. This was associated with an increased level of ceramide in the SC as assessed by Raman spectroscopy. In addition, for the deepest layer of SC, a higher level of water content was measured (14).

Considering the cumulative evidence from different published trials, it may be inferred that NTP-CE-mediated short- and long-term skin moisturization is caused by various key ingredients which act in an additive or synergistic fashion.

The results of our pediatric study showed that NTP-CE is well tolerated and improves skin hydration in infants as young as 3 months. The tolerability results are in accordance with other studies showing good tolerability of topical panthenol-containing preparations in infants (40,41). The skin hydrating effect of NTP-CE was more pronounced in infants than previously reported for healthy adults (4). This might have been due to the dryer skin in infants observed at baseline. In addition, infants in the age range of our subjects show a higher SC water content and a steeper water gradient than adults (42) which may render it possible to achieve a more pronounced moisturizing effect with NTP-CE in small children.

Appropriate SC hydration is essential not only for providing flexibility to the skin but also for regulation of all the biochemical processes occurring in the SC (22). Dry skin, independent whether it is a condition on itself or a symptom of other conditions (e.g. AD), is typically lipid-depleted (6,29,30). For instance, abnormalities in SC lipids have been confirmed in patients with AD (6). Marked reductions in the amount of ceramides have been found in lesional and non-lesional skin of AD patients (6,29). In one study, the SC levels of ceramide 1 and 3 were significantly lower in comparison with age- and sex-matched healthy subjects; the quantity of ceramide 3 was significantly correlated with impairment of transepidermal water loss (43). In addition, the ceramide/cholesterol ratio is altered in atopic skin (44).

Clinical studies showed that the daily use of emollients prevents AD or reduces flare-ups (45,46). Recently, an expert panel reached consensus that the use of appropriate emollients at all post-inflammatory AD stages has the potential to maintain skin hydration with reduced acute exacerbations of AD (1).

NTP-CE was well tolerated in our studies, consistent with historical data gathered with emollients (9). Thus, NTP-CE may become a valuable emollient providing sustained skin moisturization via SC replenishment with lipids and restoration of intercellular lamellar lipid structures, and is well tolerated by infants and adults in need for daily care of dry and sensitive skin.

A limitation of our two studies may be the recruitment of healthy subjects rather than patients with dry skin disease (e.g. AD patients). However, the use of lesional diseased skin with different degrees of involvement would provide highly variable measurements (47). Another limitation of the moisturization study was that an untreated control was used instead of placebo. However, it was not possible to control for all ingredients considered important for the skin-moisturizing effect of NTP-CE. The pediatric study was open and non-comparative. Thus, it cannot be excluded that the observed results have been influenced by study expectations. In the absence of an active comparator, no superiority claims over other emollients can be made.

Conclusions

Our results suggest that NTP-CE usage is associated with sustained skin moisturization not only short-term but also long-term as assessed by instrumental measurements in adults and infants. Results from Raman spectroscopy imply a NTP-CE-mediated relocation of the water molecules from upper to deeper layers of the SC leading to deep moisturization. In addition, twice-daily application of NTP-CE for 4 weeks was well tolerated by healthy infants as young as 3 months. The results of the two studies support the daily use of NTP-CE in subjects with dry and sensitive skin in adults as well as in the pediatric population.

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Consent

We acknowledge that study participants cannot be identified via this paper; we have fully anonymized them.

Health and safety

It is confirmed that we complied with all mandatory health and safety procedures in the course of conducting the work reported in our paper.

Disclosure statement

Hans Stettler, Peter Kurka, and Holger Lenz are employees of Bayer Consumer Care AG, Basel, Switzerland. The other authors report no conflicts of interest.

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