

Investigator-blinded, randomized, open label, monocentre, intra-individual comparison studies to investigate the long-lasting and long-term moisturization as well as skin barrier repair using a new emollient product for daily use compared to untreated skin

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Introduction

Impaired skin barrier plays a main role in various skin conditions like dry skin, sensitive skin, atopic dermatitis, and contact dermatitis. Moisturization and restoration of the stratum corneum skin barrier are therefore important properties any care product especially positioned for sensitive skin has to deliver. Two studies were performed to investigate the moisturizing properties and the effects on skin barrier restoration of a new daily care product with emollients.

Study Design

Study 1: The purpose of the first study was to assess the moisturizing properties as well as the barrier restoration effects of a new daily emollient product (Bepanthenol SensiDaily, Bayer) in subjects with dry skin. There were 4 test areas on the subjects' volar forearms which were treated differently. Two areas were challenged with 0.5% sodium dodecylsulfate solution over 24 h under occlusion, the other areas remained unchallenged. Two areas (challenged and unchallenged) were treated with the test product over three weeks followed by a regression period of 1 week. A challenged and untreated area served as a positive control. An unchallenged and untreated area served as negative control.

Study 2: The objectives of the second study were to investigate the long-lasting and long-term skin moisturization of the new daily emollient product. The long-lasting moisturization was investigated after a defined single administration of the test product over a period of 24 hours compared to an untreated area on the volar forearm. The long-term moisturization was investigated after multiple administrations over four weeks on volar forearms. In addition, the kinetics of moisturization was assessed.

Statistical tests and methods

This exploratory trial investigated several efficacy variables. Therefore, no primary and secondary variables were defined. Computation of the statistical data was carried out with a commercially available statistics program. A significance level of 0.05 (type I error alpha) was chosen for statistical analysis. Due to the explorative character of this study, no adjustment for multiplicity was done. Stratum corneum hydration was measured using corneometry (Corneometer CM 825) for measuring electrical capacitance. Dielectricity varies as a function of the skin's water content as a measure of stratum corneum hydration. The kinetics of moisturization was assessed by means of Raman spectroscopy (Skin Analyzer model 3510). Kinetics of moisturization means the assessment of the concentrations of water in defined depths of the stratum corneum over time. The skin barrier was investigated by determining transepidermal water loss (TM300) on SDS-challenged and unchallenged skin, stratum corneum lipid content and lipid lamella length using a lipid analysis method on unchallenged skin.

Study 1: Skin hydration is improved and skin barrier function is restored

Table 1:

Hydration (Day 22)	Treatment	Raw Data	Difference to BL	Mean Values (AUC)
	A	34.67	-0.15	-0.95
	B	42.15	6.23	129.23
	C	35.83	10.82	49.95
	D	42.94	19.23	274.87

An increase of skin capacitance values can be regarded as skin-moisturizing effect. Skin hydration significantly improved over 3 weeks when using test product on unchallenged skin (Table 1, treatment B, p<0.001) as well as on challenged skin (Table 1, treatment D, p<0.001) compared to untreated control.

Trans-epidermal water loss (TEWL):

Table 2:

TEWL (Day 22)	Treatment	Raw Data	Difference to BL	Mean Values (AUC)
	A	5.60	-1.32	23.25
	B	4.78	-1.68	19.83
	C	6.13	-14.30	-123.38
	D	5.10	-16.45	-168.36

An increase of TEWL values indicates an impairment of the skin barrier function. Trans-epidermal water loss was significantly decreased over 3 weeks when using test product on challenged skin (Table 2, treatment D versus C, p=0.023) compared to untreated challenged control.

Study 1: Length and Structure of Lipid Lamellas is improved

Table 3: Changes in average lipid length

Time	Treatment	Mean Values		p-Values
		Raw Data	Differences to Baseline	
Day 2 (Baseline)	A	89.593	--	--
	B	82.925	--	
Day 15	A	112.049	22.456	< 0.001 *
	B	203.277	120.352	
Day 22	A	125.446	35.853	< 0.001 *
	B	203.530	120.605	
Day 29	A	145.425	55.832	0.001 *
	B	194.427	111.502	

An increase of the length of intercellular lipid lamellae corresponds to better barrier functions of the skin. The length of lipid lamellae significantly increased from 83 nm/1000nm² to 203 nm/1000nm² after 3 weeks treatment with test product (Table 3, Day 22). This increase was significantly higher than in the untreated control area (p<0.001). Significantly longer lipid lamellae were even maintained over the one week follow-up period post use (Table 3, Day 29). Again, this increase versus baseline was significantly larger than in the untreated control area (p=0.001).

Figure 1: Length of Lipid Lamellae during 3 weeks' use and 1 week post-use



* Significant increase compared to untreated control on differences to baseline (p<0.001)

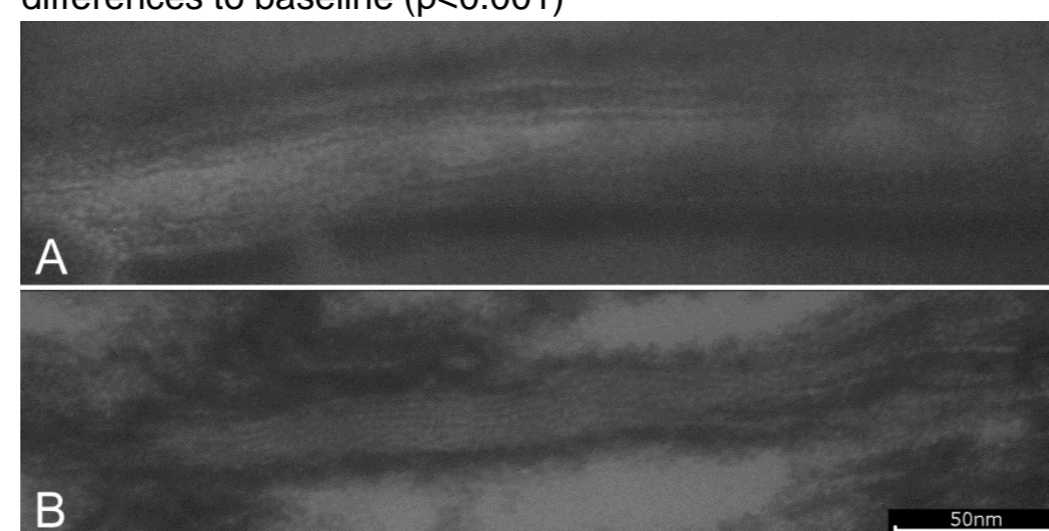


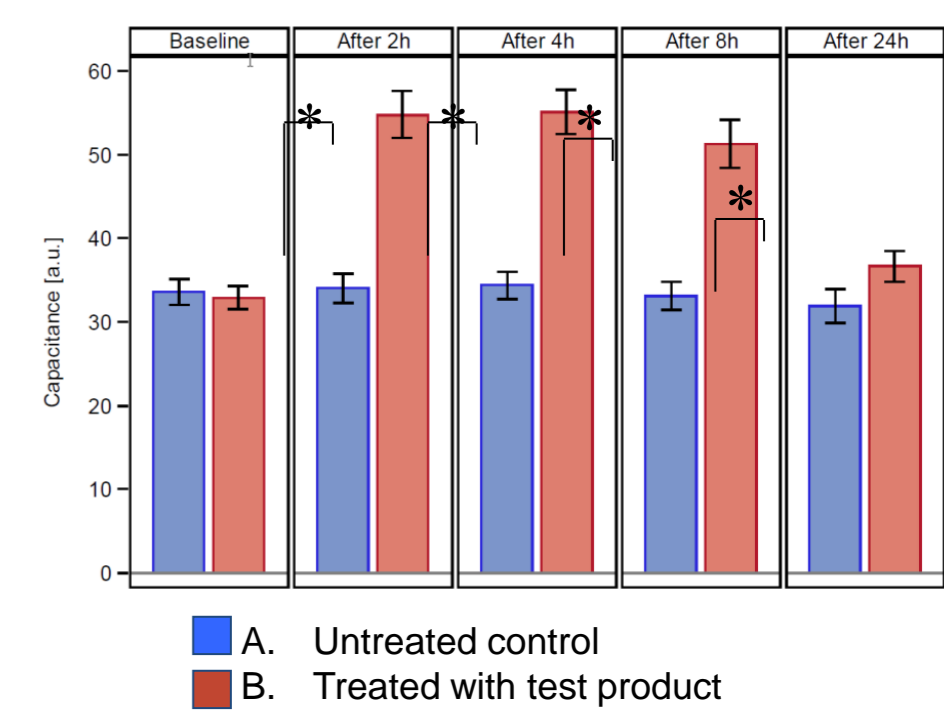
Figure 2: Lipid morphological analysis using TEM pictures at Day 29 (1 week post-use).

Study 2: Skin hydration is improved long-lasting and long-term

Long-Lasting Skin Moisturization: Short-Time Kinetics (24 h):

Dry skin is typically described as flaky and lipid-depleted. The topical application of lipids can therefore help to improve skin integrity for binding water and enhance moisturization. An increase of skin capacitance values is regarded as skin-moisturizing effect. The comparison of treatments on differences to baseline showed significantly higher skin capacitance values after treatment with product B in comparison to untreated skin (A) after 2 hours (p<0.001), 4 hours (p<0.001), 8 hours (p<0.001) as well as after 24 hours (p<0.001, Figure 3).

Figure 3: Long-lasting moisturization



Long-Term Skin Moisturization: Use Period (4 Weeks):

The comparison of treatments on differences to baseline showed significantly higher skin capacitance values after treatment with product B in comparison to untreated skin (A) after continued use over 4 weeks (p>0.001, Table 4, Day 29).

Table 4: Difference to baseline for long-lasting and long-term moisturization

Time	Differences to Baseline	
	A	B
After 2 h	0.43	21.88
After 4 h	0.76	22.23
After 8 h	-0.48	18.34
After 24 h	-1.72	3.76
24 h (AUC)	-15.90	302.03
Day 29	-2.46	5.58

These results can be explained by an improvement of the dielectricity of the upper skin layer after product application: Only a weak electrical field can be built between the measuring head of the Corneometer and dry, possibly flaky skin. After product application, the skin became smoother and greasier, thus increasing the contact area between the measuring head and the skin. This resulted in improved dielectricity, i.e. higher skin capacitance after product application.

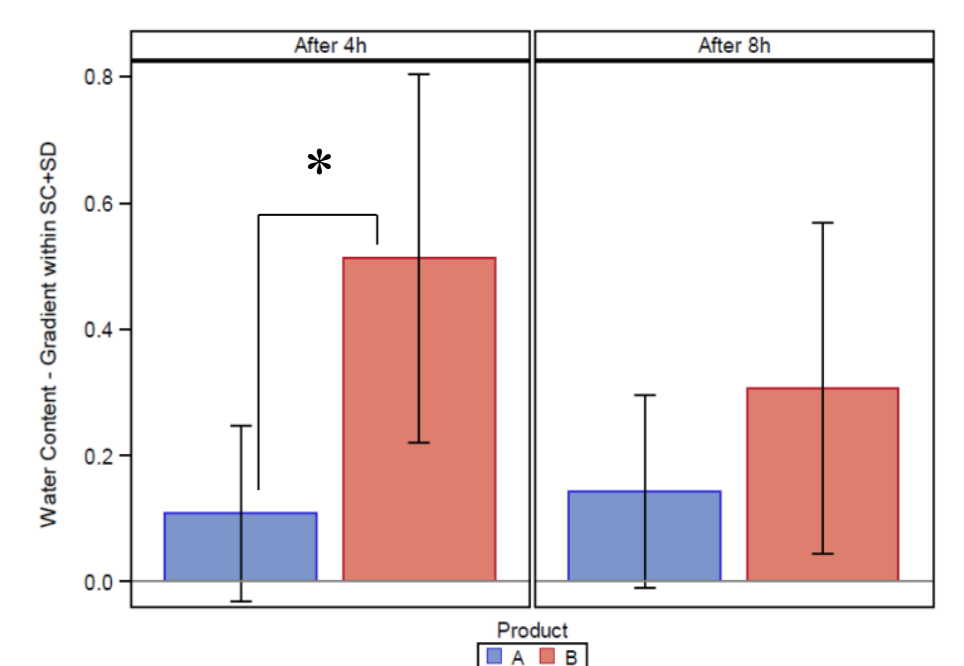
Study 2: Deep Moisturization as shown by Raman Spectroscopy

Water profile within skin:

Raman spectra are obtained by focusing low power laser light in the skin and by measuring the Raman scattered light from the laser focus. A small part of the scattered light is found at wavelengths higher than the incident laser light. This part of the scattered light provides information about the molecular composition of the skin.

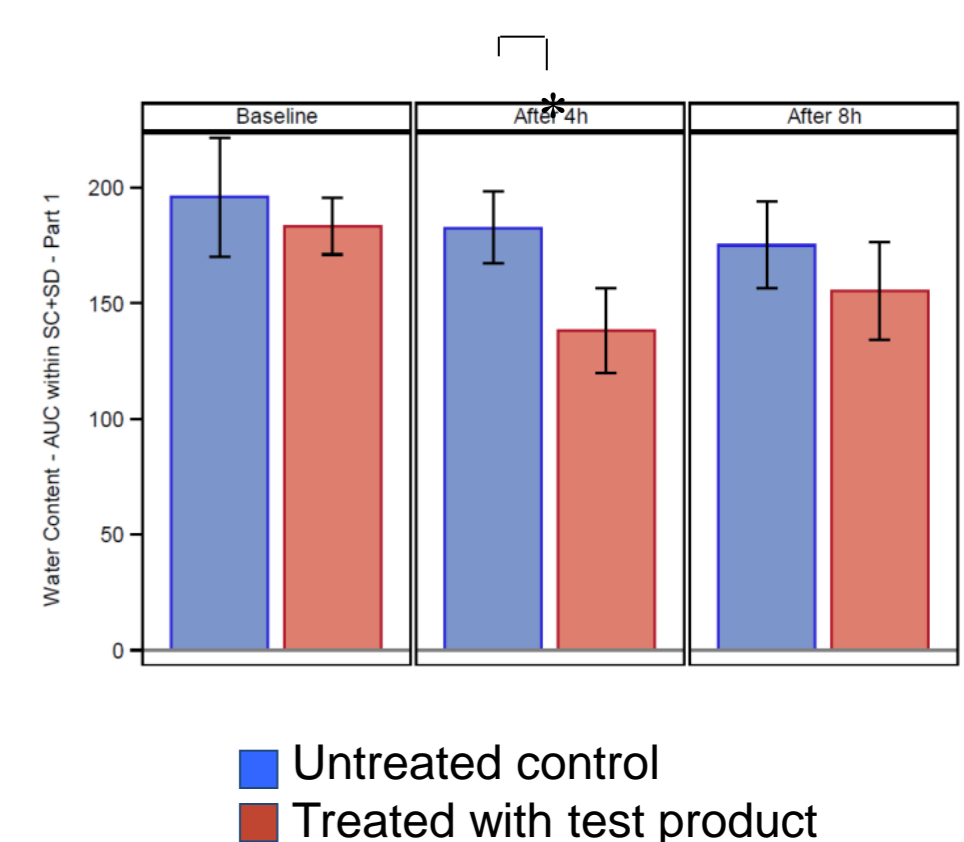
The water gradients (slope of water increase) from outer to inner stratum corneum (SC) and in a layer of 20 µm thickness below stratum corneum were calculated. The areas under the curve (AUC) were calculated for the total water content within the stratum corneum (including stratum disjunctum = SC+SD) as well as for the water content in the 20 µm layer below stratum corneum (water content in deeper layer). The stratum corneum was divided into three equally spaced parts.

Figure 4: Water Gradient within SC+SD



- Significantly lower mean values of the water content were observed on the skin surface (depth of 0 µm) 4 h (p<0.001) as well as 8 h (p=0.004) after treatment with test product in comparison to untreated skin.
- The water gradient within SC+SD was significantly higher 4 h after treatment with test product than on untreated skin (p=0.036, Figure 4).
- The parameter "AUC within SC+SD (part 1, water content in the uppermost part of SC) was significantly lower after 4 h when treated with test product (p=0.013, Figure 5).
- The AUC within the deepest part of the stratum corneum (part 3) increased 4 h, and 8 h after application of test product, while it was reduced in comparison to Baseline on untreated skin. The differences to untreated skin just missed significance (p < 0.1).

Figure 5: AUC within SC+SD, part I



The results indicate a relocation of the water molecules into deeper layers of the stratum corneum.

Safety:

Two adverse events were observed in one subject during the first study showing a few papules, erythema and itching. The subject was discontinued and recovered without sequela. These adverse events were mild to moderate. They were considered as associated with the test product. Three adverse events were observed in the second study. They were mild or moderate and resolved completely. Only one adverse event in the second study was considered as related to the study product. No serious adverse events occurred.

Conclusions:

- Definite improvements of skin capacitance and skin barrier function were demonstrated.
- Lipid lamellae were measurably longer after three weeks of test product in comparison to untreated skin indicating a better barrier function of the skin. This effect was still existent one week after the end of treatment.
- After a single application of test product, skin capacitance was significantly higher than on untreated skin for up to 24 hours showing long-lasting moisturization.
- Skin capacitance was significantly higher after application of test product over a use period of 4 weeks in comparison to untreated skin showing long-term moisturization.
- The water content within the upper part of the stratum corneum was significantly reduced and the water gradient significantly increased for up to 4 hours, indicating a relocation of the water molecules into deeper layers of the stratum corneum showing deep moisturization.
- The results demonstrate that the new emollient is supporting moisturization and skin barrier repair not only short but also long term which is especially important in patients with dry and sensitive skin.