Niacinamide-Containing Facial Moisturizer Improves Skin Barrier and Benefits Subjects With Rosacea

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A growing body of literature suggests that some moisturizers can improve stratum corneum barrier function, as well as ameliorate dry skin. The clinical signs and symptoms of rosacea, which include increased facial skin dryness and sensitivity, suggest a possible role for such moisturizers as an adjuvant in the management of this condition.

This randomized, investigator-blind, controlled observational study (N=50) was designed to assess whether a niacinamide-containing facial moisturizer would improve the stratum corneum barrier and thus provide a clinical benefit to subjects with rosacea. Subjects with rosacea applied the test moisturizer to their face and to one forearm twice daily for 4 weeks. The other forearm remained untreated as a control. Barrier function on the forearms was assessed instrumentally and using a dimethyl sulfoxide (DMSO) chemical probe. Stratum corneum hydration also was measured instrumentally. The dermatologist investigator evaluated each subject's rosacea condition over the course of the study, and subjects self-assessed their facial skin condition at study end. Instruments provided objective measures of stratum corneum barrier function and hydration on the face.

Results of tests conducted on the forearms showed that the niacinamide-containing facial moisturizer improved stratum corneum barrier function and hydration. Similar trends in these parameters were seen on the facial skin. The investigator's evaluations and subjects' self-assessments showed improvement in the signs and symptoms of rosacea over the course of the study. These results suggest that this patient population can benefit from using a facial moisturizer that improves the stratum corneum barrier.

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Moisturizers and emollients often are viewed only in the context of their ability to increase stratum corneum hydration, relieve dry skin, or improve skin characteristics such as softness and suppleness. However, a growing body of literature suggests that these products can not only play a more active role in improving skin homeostasis and deficient stratum corneum barrier function but also be useful therapeutic adjuvants in the treatment of various skin conditions. Such benefits are reported for moisturizers and emollients based on physiologic or nonphysiologic lipid systems, as well as for a number of nonlipid ingredients that are found in some products.[1-8]

The facial skin of patients with rosacea is often hyperirritable compared with that of healthy patients. A variety of exogenous insults can trigger a flare-up of symptoms such as erythema, stinging, or burning. Skin care products are commonly identified as offending agents.[9-11] Additionally, patients with rosacea often experience dry facial skin that can exacerbate subjective symptoms.[12,13] Application of moisturizers or emollients helps to ameliorate this dryness.

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The susceptibility to hyperirritability, exogenous insults, and subjective symptoms that are associated with rosacea are reminiscent of the symptomatology reported for sensitive skin.[14,15] A deficient stratum corneum barrier contributes to sensitive skin, and skin sensitivity and reactivity are reportedly decreased by treatments that improve stratum corneum barrier function.[16-18] Although there is no reported link between rosacea and a deficient stratum corneum barrier, the similar response pattern elicited by certain personal care products in patients with rosacea and sensitive skin suggests that individuals with rosacea also may benefit from an improved facial stratum corneum barrier.

This study was conducted to assess the effect of a niacinamide-containing facial moisturizing product that improves barrier function in healthy skin[19] on the stratum corneum barrier function of subjects with rosacea and to determine whether they may derive a clinical benefit from using this moisturizer.

Materials and Methods

Study Population—The study was approved by Schulman Associates Institutional Review Board, Inc. After signing informed consent, 50 healthy women (median age, 45 years) with Fitzpatrick skin type I, II, or III who regularly used a facial moisturizer were enrolled in the study. The dermatologist investigator confirmed that these subjects had advanced subtype 1 or 2 rosacea characterized by persistent erythema, telangiectases, and inflammatory lesions. Subjects using oral corticosteroids to treat their disease were excluded from the study, as were those who applied topical antiaging products, antiacne products, or corticosteroids to their face (or forearms, in the case of topical corticosteroids) within the 2 weeks prior to study enrollment. Other prescribed medications for rosacea were allowed during the study, but no change in therapy was permitted.

Treatment Products—Subjects were provided with a regular facial moisturizer (Olay® Active Hydrating Beauty Fluid - Sensitive Skin), a liquid face wash (Olay Foaming Face Wash - Sensitive Skin), and a cleansing bar (Olay Sensitive Skin Beauty Bar) at the start of a 2-week washout period. The subjects and investigator were not blinded to product identity. The subjects were instructed to apply the regular facial moisturizer to their face in the morning and evening. No moisturizer or lotion application was permitted on the forearms. Subjects used the supplied cleansers throughout the study for facial and body cleansing.

At the start of the 4-week treatment period, the subjects were switched from the regular facial moisturizer to a facial moisturizer containing 2% niacinamide (Olay Total Effects 7× Visible Anti-Aging Vitamin Complex Fragrance Free) and continued the same twice-daily application schedule. The investigator was blind to the identity of the test facial moisturizer, and the product was distributed in generic, white pump bottles labeled only with a subject number and usage instructions.

Study Design—This controlled observational study involved treatment of the face and forearms. The trial consisted of a 2-week washout period followed by a 4-week treatment phase.

Subjects applied moisturizer to their face twice daily throughout the study, but different facial

Table 1.

TEWL and Skin Capacitance Measurements*

	Least Squares Mean (SD)		
	Treated Forearm	Untreated Forearm	*P* Value
Baseline TEWL, n=31†	5.0 (1.2)	5.0 (1.2)	.89
Week 4 TEWL, n=29†	2.5 (1.7)	3.9 (1.7)	<.01
Baseline skin capacitance, n=48	29 (4.6)	28 (4.6)	.31
Week 4 skin capacitance, n=46	31 (4.9)	23 (4.9)	<.01

*TEWL indicates transepidermal water loss.
†Base size reduced because of an environmental control issue at baseline.

moisturizer products were used during the washout and treatment phases. The women were instructed to avoid excessive sun exposure and to apply their usual sunscreen product if they spent time outdoors. Facial foundation or color cosmetics were allowed except on scheduled evaluation days. Subjects washed their face with the supplied liquid face wash 1 to 2 hours before a scheduled evaluation and did not apply the test moisturizer or makeup until after the evaluation was completed.

Product application to the forearms was conducted as a bilateral comparison during the 4-week treatment phase. The niacinamide-containing facial moisturizer was randomly assigned to one dorsal forearm with the other forearm remaining untreated as a control. The investigator was blind to these assignments. Subjects applied the moisturizer to the assigned dorsal forearm surface twice daily at the same time they applied the product to their face.

Clinical Evaluation—The investigator examined each subject's face before entering the washout period to verify rosacea presence and severity and again at baseline and after 2 and 4 weeks of test moisturizer use. Erythema, telangiectases, dryness, and scaling/peeling were scored on a 4-point scale, in which 0 equaled none and 3 equaled severe, and inflammatory lesions were counted. The investigator also evaluated and scored the level of pruritus and burning experienced by subjects on the same 4-point scale. The global change in rosacea condition compared with a subject's previous visit was evaluated and scored on a 7-point scale, with +3 being markedly improved, 0 being unchanged, and −3

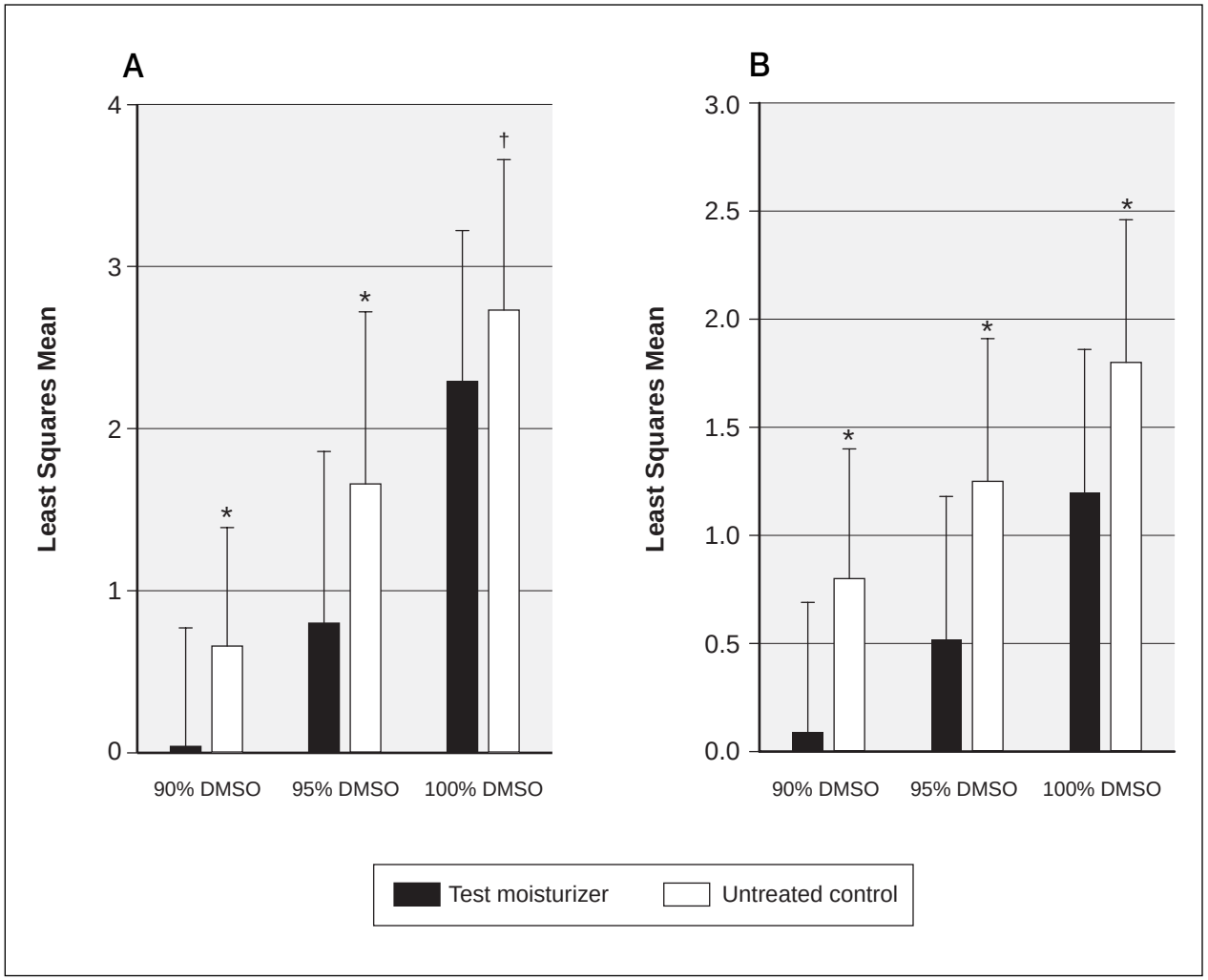

Figure 1. Least squares mean of wheal (A) and erythema (B) scores in response to 90%, 95%, and 100% (vol/vol) aqueous solutions of dimethyl sulfoxide (DMSO) applied to the dorsal forearm surface at the 4-week evaluation. The whealing score is based on a scale of 0 to 4 in which 0=none and 4=elevated tense wheal. The erythema score is based on a scale of 0 to 3 in which 0=none and 3=severe. Asterisk indicates $P<.01$; dagger, $P<.04$.

being markedly worse. The subjects were graded at the 2- and 4-week visits. Overall tolerance of the test facial moisturizer was judged at the 4-week visit.

Instrumental Assessments—Transepidermal water loss (TEWL) and skin capacitance were measured (using the DermaLab® and Corneometer CM825®, respectively) on each subject's face and forearms at baseline and at the 4-week evaluation visit to provide objective assessments of stratum corneum barrier function and hydration, respectively. Subjects acclimatized under controlled environmental conditions (70°F±2°F, 35%±5% relative humidity) for at least 30 minutes before measurement. Measurements on the face were made in the center of the left cheek approximately 5 cm from the corner of the mouth. Forearm measurements were made at the center of the dorsal surface of each arm.

Table 2.

Investigator-Assigned Mean Values for Rosacea Signs and Symptoms

	Mean Score, Count (SD)	
Signs and Symptoms	Baseline	Week 4
Erythema*	1.8 (0.7)	0.8 (0.7)
Telangiectases*	1.6 (0.7)	1.6 (0.7)
Dryness*	0.8 (0.8)	0.0 (0.2)
Scaling/peeling*	0.6 (0.8)	0.0 (0.2)
Inflammatory lesions†	2.3 (3.2)	0.5 (1.3)

*Scored on a scale in which 0=none and 3=severe.
†Sum of papule and pustule counts.

TEWL data were collected for only 31 subjects at the baseline visit because of an environmental control issue in the area in which this instrument was operated. This issue was corrected by the 4-week visit, and TEWL data were obtained for the 46 subjects who completed the study.

Chemical Probe Response—A dimethyl sulfoxide (DMSO) chemical probe provided supplemental information about forearm stratum corneum barrier function at the 4-week visit. The procedure was adapted from published methods.[20,21] Three concentrations of DMSO were prepared in water: 90%, 95%, and 100% (vol/vol). Three 12-mm circles were marked on each dorsal forearm surface and outlined with stopcock grease. At the center of each circle, 15 µL of DMSO test solution were dispensed; each site was covered with plastic disks slightly larger than the grease ring. The order of the DMSO solution placement up and down the arm was randomized on each subject. The disks were gently pressed against the skin to distribute the test solution over the site. After 5 minutes, the disks were removed, and the skin was gently wiped free of grease. The investigator recorded the wheal onset time for each DMSO concentration and scored the wheal-and-erythema responses at each site 10 minutes after disk removal. Each wheal was scored on 5-point scale in which 0 equaled none and 4 equaled an elevated tense wheal; erythema was scored on a 4-point scale in which 0 equaled none and 3 equaled severe or marked.

Subject Self-evaluation—Subjects completed a questionnaire at the 4-week visit to assess the perceived changes in 5 attributes related to the appearance of their rosacea condition: overall skin appearance, redness/blotchiness, skin tone/color, blemishes, and dryness/flakiness. Each attribute was rated on a 9-point scale, with +4 being extremely better, 0 being no change, and −4 being extremely worse.

Statistical Analysis—The mean and standard deviations were calculated for investigator-assigned scores and lesion counts and for subject self-assessment data. The latter data also were expressed as the percentage of subjects reporting improvement, no change, or worsening; and a sign test was used to compare the number of subjects reporting improvement or worsening for each rated parameter. The investigator's assessment of the global change in each subject's rosacea condition at the 2- and 4-week evaluation visits and of each subject's tolerance of the test facial moisturizer at the final visit were expressed as a percentage of the number of subjects enrolled at the time of the evaluation.

Because all subjects applied the test moisturizer to their face, inferential statistics were not run on the instrumental data collected on the cheek. Instead, the facial TEWL and skin capacitance data were averaged by evaluation visit. The forearm TEWL

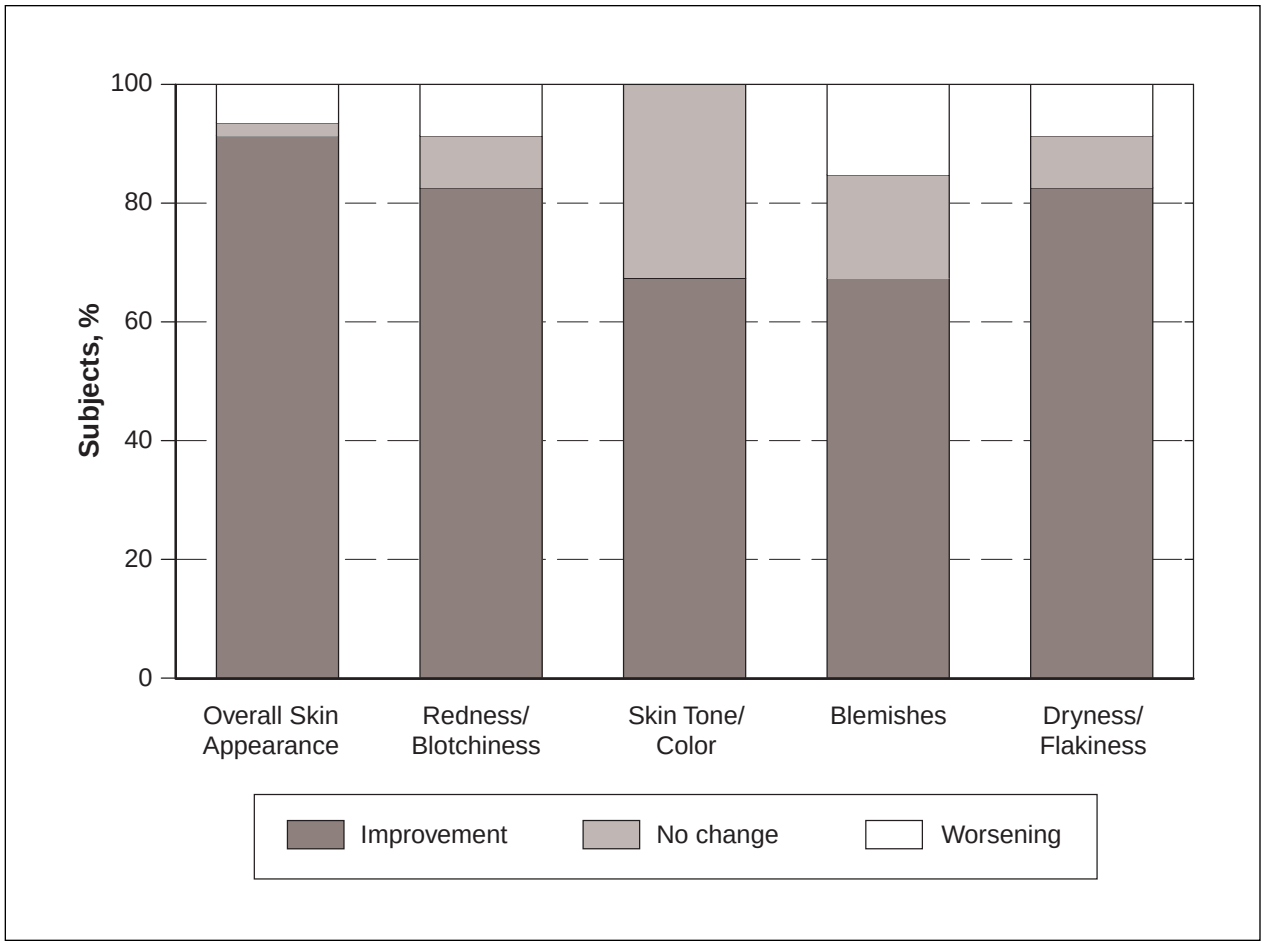

Figure 2. Percentage of subjects self-assessing improvement, no change, or worsening in skin attributes related to their rosacea. For each parameter, a significant percentage of subjects who noted a change in their skin condition perceived improvement ($P<.01$).

and skin capacitance data were analyzed using an analysis of variance model with the subject, arm, and treatment as factors and the baseline parameter value as a covariate. Only subjects with valid TEWL data at the baseline and final visits were included in the analysis. An analysis of covariance model with the subject, arm, and treatment as factors was used to analyze the chemical probe data for each DMSO concentration.

Results

Subject Accountability—Of the 50 subjects enrolled, 46 completed the study. Two subjects failed to return for the baseline evaluation and were lost to follow-up. Two subjects developed facial irritation while using the supplied washout products but continued into the treatment phase of the study. Their condition did not improve during treatment, and the investigator dropped them from the study at the 2-week evaluation.

Stratum Corneum Barrier Function—The bilateral comparison conducted on the dorsal forearms provided the primary assessment of the test moisturizer's effect on the stratum corneum barrier. TEWL measurements showed no significant barrier function difference between the treated and untreated forearms at the baseline visit ($P=.89$, Table 1); however, at endpoint, the least squares mean TEWL value for treated forearms was significantly lower than that for untreated forearms ($P<.01$), indicating that application of the niacinamide-containing moisturizer improved stratum corneum barrier function. The mean wheal-and-erythema responses on treated forearms were significantly lower compared with untreated forearms across the range of DMSO concentrations ($P\leq.04$, Figure 1). The whealing response developed more slowly on treated forearms than on untreated forearms for the 90% and 95% DMSO concentrations, but onset times were

comparable for the 100% DMSO concentration (data not shown).

The mean TEWL measured on the subjects' cheeks at baseline was 13.9 $g \cdot m^{-2} \cdot h^{-1}$ (SD=6.3). This mean value decreased to 9.2 $g \cdot m^{-2} \cdot h^{-1}$ (SD=4.3) at the endpoint evaluation.

Stratum Corneum Hydration—There was no significant difference between mean baseline skin capacitance values made on the treated and untreated dorsal forearms ($P=.31$, Table 1). At endpoint, forearms treated with the niacinamide-containing facial moisturizer were significantly more hydrated than the control forearms ($P<.01$). The mean skin capacitance values measured on the face increased from 58.7 arbitrary units (SD=10.5) at baseline to 62.1 arbitrary units (SD=10.7) at the endpoint evaluation.

Clinical Response—Facial erythema is the hallmark of rosacea, particularly in the early stages of the disease. Thus, it is not surprising that of the 4 subjective symptoms scored by the investigator, facial erythema was scored highest at the baseline visit (Table 2). There was a marked decrease in erythema severity over the 4-week treatment phase. Telangiectases remained unchanged over the course of the study. Using the niacinamide-containing facial moisturizer also improved dryness and scaling/peeling and decreased inflammatory lesion counts.

The investigator's global assessment of rosacea paralleled the scoring of the individual parameters. After 2 weeks of using the facial moisturizer, 79.2% (38/48) of subjects showed global improvement; after 4 weeks, 95.7% (44/46) showed global improvement. The investigator judged that the facial moisturizer was well tolerated by all subjects who completed the study.

Subject Self-assessment—Most subjects in this study perceived a change in the appearance of their facial skin condition over the course of treatment; of these subjects, a significant percentage perceived improvement ($P<.01$, Figure 2).

Comment

The TEWL measurements taken from the forearms of subjects with rosacea in the present study were consistent with those reported in a previous study conducted on healthy skin,[19] which showed that the niacinamide-containing facial moisturizer improved barrier function. The agreement between TEWL values in these studies indicates that stratum corneum barrier function on the dorsal forearm is not compromised in patients with rosacea. An improved stratum corneum barrier should be more resistant to penetration by noxious stimuli; this is reflected in the reduced response on moisturizer-treated skin in the DMSO challenge.

The trend in baseline and endpoint TEWL values measured on the cheek paralleled the trend observed on the forearm, suggesting that facial stratum corneum barrier function also improved as a result of applying the niacinamide-containing moisturizer. The mean TEWL value measured on the cheeks of rosacea subjects in the present study was somewhat higher than the mean value reported for healthy skin in a study by Tagami et al.[22] This suggests a possible role for stratum corneum barrier compromise in the heightened skin sensitivity that is often observed with rosacea.

Skin capacitance values showed the expected trend for a quality moisturizer, ie, at endpoint, treated forearms were more hydrated than control forearms ($P<.01$), and the mean skin capacitance values measured on the face increased over the course of the study. In the latter case, the absence of a control does not allow us to draw an absolute conclusion about the change in facial hydration, but the parallel trends shown on treated face and forearms suggest that the test facial moisturizer increased stratum corneum hydration at both body sites.

The clinical response assessed by the investigator and subjects mirrored the changes in skin condition shown by the objective endpoints. The reduction in facial erythema observed among these subjects is consistent with improved stratum corneum barrier function; from this we infer a possible role for a barrier defect in the persistence of erythema in rosacea by allowing low-grade irritants to penetrate the skin more readily. Improvement in clinical dryness and scaling, an expected outcome of using a quality moisturizer, is consistent with the increase in stratum corneum hydration shown by skin capacitance measurements. The improvement in these clinical parameters is reflected in the subjects' assessments of the change in the appearance of their facial skin condition over the course of treatment. Of the signs and symptoms assessed, only the number of telangiectases remained unchanged; however, it is not expected that a facial moisturizer would affect this symptom.

Conclusion

Instrumental and chemical probe challenge endpoints demonstrate the ability of the test facial moisturizer to improve stratum corneum barrier function. There was a parallel improvement and mitigation of rosacea signs and symptoms shown by investigator and subjects' assessments. These results suggest that patients with rosacea can

benefit by adding a facial moisturizer that improves the stratum corneum barrier to their regular skin therapy, and we think this hypothesis warrants further study in a controlled trial.

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