ORIGINAL RESEARCH

A Novel Night Moisturizer Enhances Cutaneous Barrier Function in Dry Skin and Improves Dermatological Outcomes in Rosacea-prone Skin

by FRANCINE SANTORO, MD, and SANDRINE TEISSEDRE, MSc

Dr. Santoro is with Galderma Research and Development in Egerkingen, Switzerland. Dr. Teissedre is with Galderma Research and Development in Sophia Antipolis, France.

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ABSTRACT

Objective: We assessed whether Cetaphil Redness Control Night Cream (CRCNC; Galderma Laboratories, Fort Worth, Texas) improves electrical capacitance (EC) and transepidermal water loss (TEWL) in healthy subjects with dry skin and determined efficacy and tolerability in subjects with rosacea. **Study design:** The present study included two independent, open-label investigations: in the first, EC and TEWL were measured at baseline and at two, four, eight, and 24 hours after one application of CRCNC to dry skin; in the second, an evaluation of once-daily CRCNC application for 22 days using a chromameter, image analysis, and trained rater was performed, with patient evaluations at baseline and Days 1, 8, and 22 collected. The first study enrolled 20 subjects (13 women; mean age: 45 years). The second study enrolled 33 women (mean age: 54 years), with 30 having sensitive skin. **Results:** EC increased significantly at two (by 67.0%), four (60.2%), eight (52.1%), and 24 (17.9%) hours after CRCNC application. TEWL was reduced significantly at two (18.0%), four (14.3%), and eight (18.2%) hours after application. Additionally, improvements in redness were seen at Days 8 (24.2%; p=0.008) and 22 (27.3%; p=0.004). Versus baseline, 21.2% (p=0.07), 39.4% (p<0.001), and 48.5% (p<0.001) of subjects reported improvements at 30 minutes after application and on Days 8 and 22, respectively. **Conclusions:** CRCNC is an effective and well-tolerated moisturizer that improves cutaneous barrier function in subjects with dry skin and in those subjects with sensitive skin and type 1 rosacea.

KEYWORDS: Moisturizer, patient-reported outcomes, rosacea, rosacea treatment, sensitive skin, TEWL

Rosacea is a common dermatological disorder, especially among Caucasians. Generally, the prevalence in Caucasians is at least 10 percent,[1] but it might reach up to 22 percent in some populations.[2] Rosacea, however, also occurs in people of Asian, Latin American, African American, and African ethnicity.[1] The chronic inflammation that underlies rosacea results in several symptoms that can undermine health-related quality of life (HRQoL).[3–6]

Recently updated criteria from the United States National Rosacea Society suggests that centrofacial erythema or phymatous changes, or both, are diagnostic. In addition, subjects can develop a range of major and minor cutaneous signs, including papules and pustules, flushing, telangiectasia, and ocular manifestations that appear with or without centrofacial erythema or phymatous changes.[1] The chronic inflammation that causes rosacea also seems to increase the risk of several comorbidities including certain gastrointestinal disorders such as inflammatory bowel disease, as well as some allergies and Parkinson's disease.[7–9]

As rosacea affects the face, the condition can have a marked psychological impact and undermine HRQoL.[3–6] A meta-analysis of seven studies reported that 43.0 percent and 19.8 percent of subjects with rosacea had at least moderately and severely impaired HRQoL, respectively. Moreover, 62.0 percent and 47.8 percent of people with severe rosacea reported that the condition affected social and work life "at least somewhat," respectively.[5]

Against this background, the global Rosacea Consensus (ROSCO) panel recommends tailoring treatment to the phenotype and that all subjects should participate in general skincare practices.[10] The ROSCO panel also suggests that general skincare is the main strategy to manage secondary features, such as dry appearance and sensation, and stinging.[10] Skincare methods suggested by the ROSCO panel include using gentle over-the-counter cleansers, avoiding triggers, and performing frequent application of moisturizers.[10]

Moisturizers developed for sensitive, easily irritated, rosacea-prone skin are an important element in skincare.[2] For instance, the inflammation that underlies rosacea can compromise barrier function, which, in turn, increases transepidermal water loss (TEWL) and leaves skin dry and sensitive.[2] Many subjects with rosacea report that dry facial skin can exacerbate symptoms and lead to scaling, peeling, burning, and stinging.[2,11] Moisturizers can repair and maintain stratum corneal barrier function, enhance skin hydration, reduce the

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CORRESPONDENCE: Francine Santoro, MD; Email: francine.santoro@galderma.com

likelihood of skin irritation, improve softness and suppleness, and can be adjuvants to other rosacea therapies.[11]

A moisturizer's effects should persist for 24 hours in subjects with rosacea to ensure the skin remains hydrated throughout the day, especially as several aspects of dermatological physiology exhibit circadian variations. Skin blood flow is low in the morning and peaks once in the afternoon and again in the late evening just before sleep. During the night, the rate of recovery of barrier function is slower, barrier permeability is higher, and moisture loss is higher than during the day, although the pattern varies between studies, probably reflecting the influence of other factors such as age, ethnicity, and sex.[12] Therefore, moisturizers need to be formulated specifically for use at night to support the repair of barrier function and to optimize moisturization.

Against this background, this paper reports results from two independent, open-label studies that assessed the novel product Cetaphil Redness Control Night Cream (CRCNC; Galderma Laboratories, Fort Worth, Texas). The first study aimed to determine whether CRCNC improves hydration and barrier function in otherwise healthy subjects with dry skin. The second study aimed to assess the efficacy and tolerability of CRCNC in subjects presenting with type 1 rosacea.

METHODS

The two independent, open-label studies were conducted in accordance with the Declaration of Helsinki, revised in 2013 as well as Good Clinical Practice and local regulatory and ethical requirements. All subjects provided written informed consent. Safety was monitored via the reporting of adverse events. Room humidity and temperatures were maintained within published guidelines.[13] Subjects rested in the room for at least 30 minutes before measurements.

Study A (cutaneous barrier function). The first study, performed by Institut d'Expertise Clinique (Lyon, France), enrolled healthy Caucasian adults (18–70 years old) with dry skin on their inner forearm, defined as moisturization corresponding to electrical capacitance (EC) value less than or equal to 50 arbitrary units (au). The test site did not exhibit irritation or any other dermatological abnormality.

Measurements of EC were performed using a Corneometer CM 825 (Courage & Khazaka, Köln, Germany). The au values (scale from 0 to about 130au) indicate the degree of moisturization in the upper layers of the epidermis. TEWL was measured using a Tewameter TM 300 (Courage & Khazaka, Köln, Germany). EC and TEWL were measured at baseline and at two, four, eight, and 24 hours after a single application of CRCNC. Corneometry and TEWL measurements were performed in standard conditions of temperature and humidity.

Subjects with rosacea often present with a defective skin barrier and therefore an increased TEWL.[14,15] Healthy subjects with dry skin were used in order to "mimic" the damaged barrier and increased TEWL that is found in subjects with rosacea.[14,15] The application on the forearms provides a convenient control nontreated area.

The test and control areas were distinct 20cm^2 areas on the inner forearm. A technician applied CRCNC (2mg/cm^2) to the test area on the right or left forearm according to randomization and massaged the area until the product penetrated completely.

Descriptive statistics summarized the results and differences were assessed using the Shapiro–Wilk test (significance defined as $p<0.01$). Treated and control areas were compared using a Student's t-test or Wilcoxon signed-rank test (both two-tailed, significance defined as $p<0.05$) for normal and nonparametric distributions, respectively.

Study B (efficacy and tolerability). The open-label study, performed by the proDERM Institute for Applied Dermatological Research (Hamburg, Germany), enrolled either male or female subjects with type 1 rosacea that was characterized by mild-to-moderate nontransient erythema. Subjects were between 25 years and 75 years of age, with a maximum of 20 percent of the cohort being older than 60 years of age and with at least 50 percent self-reporting sensitive skin. Patients with no dryness or redness at baseline were included in the study.

Exclusion criteria included pregnancy or lactation, conditions that might influence the test reaction or evaluation, topical medication application on the test area during the four weeks before and during the study, and active skin disease other than rosacea in the test area. The study also excluded subjects taking systemic immunosuppressive drugs (e.g., corticosteroids), antihistamines, or antibiotics within the four weeks before and during the study. Subjects who used systemic anti-inflammatory agents or analgesics (except for minor analgesics, e.g., acetylsalicylic acid or paracetamol) within the three days before and during the study were additionally excluded. Furthermore, people with documented allergies to cosmetic products and/or ingredients and eye diseases (e.g., allergic conjunctivitis) that were likely to interfere with ophthalmological evaluation were excluded.

Subjects applied CRCNC to their face, not only the lesional areas, once daily in the evening at home. A technician at the study site supervised the first application. Subjects applied CRCNC at least 10 to 16 hours before the final scheduled visit on Day 22. Each subject acted as their own control: measurements on the target area on the right cheek were compared with a control area on the forehead.

Measurements using a chromameter (CR 300 or CR 400; Minolta, Langenhagen, Germany) were performed on the middle of the right cheek and a control area on the forehead. A full-face image was taken using VISIA-CR BOOTH (Canfield Clinical Systems, Fairfield, New Jersey), which offers standardized, computer-controlled facial photography. Image analysis of skin color (a*-value, which corresponds to increased skin redness) was performed using cross-polarized light.

A trained rater assessed redness at baseline and on Days 1, 8, and 22 as well as tolerability (e.g., dryness, scaling, fissures, papules, pustules, edema, vesicles, weeping) at baseline and on Day 22. Subjects rated their agreement with statements about efficacy and traits at 30 minutes after application on Days 1 and 22 (statements are shown in the Results section). Redness was self-assessed at baseline on Days 1, 8 and 22; additionally, patient-reported efficacy (tension/tightness, feeling of dryness), patient-reported tolerability (itching, burning, tickling), and patient-reported eye status (itching, burning, sand grain feeling) were assessed at 30 minutes after CRCNC application at baseline, on Days 1 and 22.

The trained rater and subjects assessed skin redness using a five-point scale and assigned a numerical value as follows: 0=none, 0.5=very slight, 1=slight, 2=moderate, and 3=strong. The rater assessed skin dryness and objective skin status using this five-point scale. Subjects used the same scale to evaluate patient-

reported efficacy, tolerability, and eye status and rated their agreement with statements about product efficacy and traits using a five-point scale ranging from "fully agree" to "fully disagree."

Statistical significance was defined as $p<0.05$. Rater-assessed outcomes were compared using the Wilcoxon signed-rank test. The Binomial test compared frequencies of answers between the "agree" and "disagree" groups, after excluding "neither … nor" responses. Instrumental measurement parameters were compared using a paired t-test. As this was an exploratory study, the results were not adjusted for multiplicity. Statistical analyses were performed using SAS for Windows (SAS Institute, Cary, North Carolina).

RESULTS

Study A (cutaneous barrier function). This study enrolled 20 subjects (13 women; mean age: 45 years; range 18–70 years), all of whom completed the study. Baseline EC or TEWL did not differ significantly between the control and treated areas. EC increased significantly at two (by 67.0%), four (60.2%), eight (52.1%), and 24 (17.9%) hours after application of CRCNC versus at baseline (Table 1). TEWL was significantly lower at two (18.0%), four (14.3%), and eight (18.2%) hours after application of CRCNC versus at baseline (Table 1). These results reflect a long-lasting skin moisturization with a prolonged improvement of skin barrier function.

Study B (efficacy and tolerability). This study enrolled 33 female subjects with rosacea (mean age: 54.4±8.8 years). Thirty subjects (90.9%) reported having sensitive skin. All subjects completed the study. One patient developed an adverse reaction (mild diarrhea), which was unrelated to the study product and which resolved spontaneously. Subjects used a mean of 14.0g of CRCNC during this three-week study.

Table 2 summarizes the trained rater assessment of skin redness. All subjects showed some redness of the facial skin throughout the study. However, skin redness was less intense on Days 8 and 22 as compared with at baseline and at 30 minutes after application on Day 1. The proportion of subjects with moderate or severe skin redness declined from 60.6 percent at baseline to 33.3 percent at Day 22 ($p=0.008$), while the proportion of subjects with no, very slight, or slight redness increased from 39.4 to 66.7 percent.

TABLE 1. TEWL and electrical capacitance following a single application of CRCNC

MEASURE	TIME	MEAN±STANDARD DEVIATION		*P* VALUE
		CONTROL AREA	CRCNC AREA	
TEWL (gm^{-2}/h^{-1})	Initial measurement (T0)	7.4±1.7	7.7±2.3	0.502
	2 hours	7.0±1.8	5.9±1.5	n/a
	4 hours	7.4±1.5	6.6±1.8	n/a
	8 hours	7.4±1.6	6.3±1.9	n/a
	24 hours	7.2±1.7	7.0±1.9	n/a
	Difference between 2 hours and T0	−0.4±1.1	−1.8±1.9	0.006
	Difference between 4 hours and T0	0.0±1.1	−1.0±1.1	0.001
	Difference between 8 hours and T0	0.0±1.1	−1.3±1.1	0.001
	Difference between 24 hours and T0	−0.2±1.1	−0.7±1.4	0.106
Electrical capacitance (arbitrary units)	Initial measurement (T0)	31.3±7.4	30.9±6.6	0.608
	2 hours	32.1±7.6	52.4±10.5	n/a
	4 hours	32.1±8.4	50.3±10.3	n/a
	8 hours	31.4±8.0	47.1±9.4	n/a
	24 hours	33.6±7.8	38.7±7.5	n/a
	Difference between 2 hours and T0	0.8±2.3	21.5±8.2	<0.001
	Difference between 4 hours and T0	0.7±1.7	19.4±7.3	<0.001
	Difference between 8 hours and T0	0.1±1.9	16.2±5.6	<0.001
	Difference between 24 hours and T0	2.3±3.0	7.8±4.6	<0.001

CRCNC: Cetaphil Redness Control Night Cream; TEWL: transepidermal water loss; n/a: not applicable

No patient showed worsened (increased) skin redness at any time point, based on rater assessment. However, 6.1 percent showed an improvement (reduced redness) as compared with at baseline 30 minutes after application ($p=0.500$). Furthermore, 24.2 and 27.3 percent of subjects, respectively, showed improvements at Day 8 ($p=0.008$) and Day 22 ($p=0.004$).

All subjects reported some facial skin redness throughout the study, which was less intense on Days 8 and 22 as compared with at baseline and 30 minutes after application on Day 1 (Table 2). The proportion of subjects who self-assessed their skin redness as moderate or severe declined from 87.9 percent at baseline to 42.4 percent on Day 22 ($p<0.001$), while the proportion with no, very slight, or slight redness increased significantly from 12.1 to 57.6 percent. Only one patient (3.0%) reported a worsening in their skin redness versus at baseline at 30 minutes after application and on Day 22 (but not on Day 8). However, 21.2 percent reported an improvement as compared with at baseline at 30 minutes after application ($p=0.07$). Moreover, 39.4 percent and 48.5 percent of subjects showed improvements at Days 8 and 22, respectively (both $p<0.001$).

Mean a*-values increased significantly, indicating increased skin redness, between baseline and Day 22 on the forehead (mean change: 1.46 a* units) and cheeks (mean change: 0.96 a* units). The difference between the two sites at Day 22 was statistically significant (Table 3).

In comparison with at baseline, mean a* values for erythema assessed using chromameter were higher at 30 minutes after application on Days 1 and 22. Values were significantly lower on Day 8 versus at 30 minutes after application on Day 1 and significantly higher on Day 22 as compared with on Day 8 (Table 3). However, these variations were not reflected in either the rater or subject assessment of redness.

CRCNC produces a rapid improvement in patient-reported outcomes in rosacea skin. For instance, 30 minutes after application, 78.8

TABLE 2. Efficacy of CRCNC

SKIN REDNESS ASSESSMENT	TIME	NONE (VALUE: 0.0)	VERY SLIGHT (VALUE: 0.5)	SLIGHT (VALUE: 1.0)	MODERATE (VALUE: 2.0)	STRONG (VALUE: 3.0)	MEAN VALUE	*P* VALUE: MEAN VALUE VERSUS		
								BASELINE	DAY 1, 30 MINUTES PA	DAY 8
Skin redness assessed by the trained rater	Baseline	0.0%	0.0%	39.4%	60.6%	0.0%	1.6	n/a	n/a	n/a
	Day 1, 30 minutes PA	0.0%	3.0%	42.4%	42.4%	12.1%	1.7	0.688	n/a	n/a
	Day 8	0.0%	18.2%	45.5%	30.3%	6.1%	1.3	0.019	0.012	-
	Day 22	3.0%	12.1%	51.5%	27.3%	6.1%	1.3	0.008	0.001	0.739
Skin redness assessed by subjects	Baseline	0.0%	0.0%	12.1%	66.7%	21.2%	2.1	n/a	n/a	n/a
	Day 1, 30 minutes PA	0.0%	0.0%	30.3%	51.5%	18.2%	1.9	0.092	n/a	n/a
	Day 8	0.0%	3.0%	48.5%	45.5%	3.0%	1.5	<0.001	0.009	n/a
	Day 22	0.0%	15.2%	42.4%	27.3%	15.2%	1.5	<0.001	0.003	0.874

SKIN REDNESS ASSESSMENT	TIME	SUM		*P* VALUE
		NONE, VERY SLIGHT OR SLIGHT	MODERATE OR STRONG	
Skin redness assessed by the trained rater	Baseline	39.4%	60.6%	0.296
	Day 1, 30 minutes PA	45.5%	54.5%	0.728
	Day 8	63.6%	36.4%	0.163
	Day 22	66.7%	33.3%	0.080
Skin redness assessed by subjects	Baseline	12.1%	87.9%	<0.001
	Day 1, 30 minutes PA	30.3%	69.7%	0.035
	Day 8	51.5%	48.5%	1.000
	Day 22	57.6%	42.4%	0.487

CRCNC: Cetaphil Redness Control Night Cream; PA: postapplication; n/a: not applicable

TABLE 3. Skin redness assessed by image analysis and chromameter

TEST AREA	TIME	MEAN VALUE	*P* VALUE VERSUS		
			BASELINE	DAY 1, 30 MINUTES PA	DAY 8
Image analysis (a* value; arbitrary units)					
Cheek	Baseline	21.543	n/a	n/a	n/a
	Day 22	22.502	0.008	n/a	n/a
Forehead	Baseline	15.450	n/a	n/a	n/a
	Day 22	16.906	<0.001	n/a	n/a
Difference between cheek and forehead	Baseline	6.093	n/a	n/a	n/a
	Day 22	5.596	0.014	n/a	n/a
Chromameter (a* value; arbitrary units)					
Cheek	Baseline	19.406	n/a	n/a	n/a
	Day 1, 30 minutes PA	19.813	0.114	n/a	n/a
	Day 8	19.085	0.429	0.031	n/a
	Day 22	20.306	0.058	0.171	<0.001

PA: postapplication; n/a: not applicable

percent of subjects agreed that CRCNC "leaves my skin soft and smooth" and "reduces the feeling of discomfort," while 66.7 percent agreed that CRCNC "has a soothing effect'." Significantly more subjects agreed than disagreed with these statements (Table 4).

The patient-reported benefits were sustained up to Day 22. For example, 84.8 percent of subjects agreed that CRCNC "leaves my skin soft and smooth," 75.8 percent agreed that CRCNC "produces continuous moisture overnight," 75.8 percent agreed that CRCNC "is suitable for sensitive skin," and 78.8 percent said that their skin feels "nourished." Moreover, 66.7 percent of subjects liked CRCNC "very much." Significantly more subjects agreed than disagreed with these statements as well as those stating that CRCNC "has a soothing effect," "reduces the feeling of discomfort," and that their skin feels "refreshed the next morning" (Table 4).

TABLE 4. Patient-reported questionnaire results

TIME POINT	STATEMENT	DISAGREEMENT	NEITHER... NOR	AGREEMENT	*P* VALUE *
Day 1, 30 minutes after application	The product has a soothing effect	6.1%	27.3%	66.7%	<0.001
	The product leaves my skin soft and smooth	3.0%	18.2%	78.8%	<0.001
	The product immediately calms redness	24.2%	48.5%	27.3%	1.000
	The product visibly improves my skin tone	9.1%	63.6%	27.3%	0.146
	The product reduces the feeling of discomfort	6.1%	15.2%	78.8%	<0.001
Day 22	The product has a soothing effect	12.1%	27.3%	60.6%	0.002
	The product leaves my skin soft and smooth	6.1%	9.1%	84.8%	<0.001
	The product immediately calms redness	24.2%	33.3%	42.4%	0.286
	The product visibly improves my skin tone	24.2%	30.3%	45.5%	0.210
	The product reduces the feeling of discomfort	9.1%	21.2%	69.7%	<0.001
	The product produces continuous moisture overnight	6.1%	18.2%	75.8%	<0.001
	The product is suitable for sensitive skin	12.1%	12.1%	75.8%	<0.001
	I feel my skin is nourished	9.1%	12.1%	78.8%	<0.001
	I feel my skin is refreshed the next morning	12.1%	24.2%	63.6%	<0.001
	Overall, I like the product very much	21.2%	12.1%	66.7%	0.008

* Comparing the relative frequencies of disagreement and agreement excluding the "neither... nor" category

CRCNC was well-tolerated. Based on trained rater assessment, one patient showed papules at baseline and Day 22. No subjects showed fissures, pustules, edema, vesicles, or weeping (Table 5). On Day 22, in comparison with at baseline, the severity of dryness assessed by the trained rater significantly decreased, with the percentage of no, very slight, and slight redness increasing from 39.4 to 60.6 percent, while the percentage of moderate and severe dryness decreased from 60.6 to 39.4 percent (Table 6). Patient-reported feelings of dryness and tension showed a rapid and sustained degree of improvement. The proportion of subjects who reported no dryness significantly increased from 30.3 percent at baseline to 81.8 percent at Day 22 ($p<0.001$). Furthermore, the proportion of subjects who reported no tension significantly increased from 39.4 percent at baseline to 75.8 percent at Day 22 ($p=0.003$).

The proportion of subjects who self-reported improvements in the feeling of dryness as compared with at baseline was 68.8 percent at 30 minutes after application and 51.5 percent at Day 22 (both $p<0.001$). The proportion of subjects who self-reported an improvement in the feeling of tension was 56.3 percent at 30 minutes after application versus at baseline ($p<0.001$) and 39.4 percent at Day 22 versus at baseline ($p=0.002$). Single cases of itching, burning, and tickling were reported.

At baseline, three subjects self-reported ocular itching (mean value: 0.2). No cases were reported on Day 22. Single cases of burning (baseline) and sand grain feeling (Day 22) were reported.

DISCUSSION

Education and instruction about general skincare is "essential" for all subjects with rosacea to ensure the best possible treatment outcomes.[2,10] Elements in skincare include avoiding known triggers and using moisturizers developed for the sensitive, easily irritated skin of subjects with rosacea.[2] The two independent studies presented in this paper show that the CRCNC is suitable as part of the skincare regimen for subjects with rosacea, enhances cutaneous barrier function, and improves other patient-reported and objective outcomes.

The first study enrolled healthy adults presenting with dry skin on their forearms. A single application of CRCNC significantly improved moisturization of the upper epidermis. This benefit persisted for at least 24 hours after a single application. CRCNC led to a statistically significant decrease in TEWL that lasted for eight hours, which is consistent with enhanced barrier function. The study that enrolled subjects with rosacea confirms these findings. The significant improvements in dryness assessed by the trained rater and patient-reported outcomes on Day 22 compared with baseline are consistent with increased hydration of the stratum corneum.[11]

The enhanced skin function exemplified by the improved EC and TEWL seem to translate into improved outcomes in subjects with type 1 rosacea characterized by mild-to-moderate nontransient erythema. Most subjects continued to exhibit red skin throughout the study, as evaluated by the trained rater and patient-reported assessment as well as by image analysis and erythema assessed by chromameter. However, based on evaluations by the trained rater and subjects, skin redness improved between baseline and Day 22. Subjects with dry skin were used for the TEWL study. Subjects with rosacea often present with a defective skin barrier and therefore an increased TEWL. Accordingly, subjects with dry skin on the forearms were used in order to "mimic" the damaged barrier and increased TEWL that is found in subjects with rosacea.[14,15] The application on the forearm provides a convenient nontreated control area.

Patient-reported benefits emerged rapidly. For example, 78.8 percent of subjects agreed

TABLE 5. Tolerability assessments

ASSESSOR	PARAMETERS	COUNTS>0		MEAN VALUE	
		BASELINE	DAY 22	BASELINE	DAY 22
Trained rater	Dryness	20	13	0.6	0.4
	Scaling	7	4	0.1	0.1
	Fissures	0	0	0	0
	Papules	1	1	0	0
	Pustules	0	0	0	0
	Edema	0	0	0	0
	Vesicles	0	0	0	0
	Weeping	0	0	0	0

ASSESSOR	PARAMETERS	COUNTS>0			MEAN VALUE		
		BASELINE	DAY 1, 30 MINUTES PA	DAY 22	BASELINE	DAY 1, 30 MINUTES PA	DAY 22
Subjects	Itching	3	1	2	0.1	0.0	0.0
	Burning	2	0	1	0.0	0.0	0.0
	Tension	20	2	8	0.8	0.0	0.3
	Tickling	1	2	1	0.1	0.1	0.0
	Feeling of dryness	23	0	6	0.9	0.0	0.3

Scale: 0=none, 0.5=very slight, 1=slight, 2=moderate, 3=strong; PA: postapplication

that CRCNC "leaves my skin soft and smooth" and "reduces the feeling of discomfort" at 30 minutes after application on Day 1. Furthermore, 66.7 percent of subjects with rosacea agreed that CRCNC "has a soothing effect" at this time. Moreover, at 30 minutes after application on Days 1 and 22, the number of subjects who reported tension and feelings of dryness was reduced. The mean values were also lower in comparison with those at baseline.

The increase in the a*-value on image analysis and chromameter reported in this study, however, corresponds to an increase in skin redness. The reasons for the discordance between the patient-reported outcomes and rater assessments and the results of the image analysis and chromameter require further investigation. However, rosacea is characterized by a marked psychosocial impact[3–6] and several of the main symptoms are predominately subjective. Therefore, the evaluation of treatments for rosacea needs to encompass not only objective clinical effectiveness and assessments of tolerability but also capture the subjective benefits.[16]

Subjects showed a strong agreement with statements about favorable traits and attributes, which confirms the efficacy and suggests that CRCNC would be an effective adjuvant to other rosacea treatments. Notably, three-quarters of subjects liked CRCNC "very much." A well-accepted product is likely to help ensure good adherence, especially during long-term use, although further studies with longer follow up are needed. However, the amount of CRCNC applied during the study corresponds to expected use, suggesting that subjects adhered with treatment.

Many subjects with rosacea experience heightened dermatological sensitivity with skincare and personal hygiene products[14] and report that dry facial skin can exacerbate symptoms.[11] Despite enrolling 90.9 percent of subjects with self-reported sensitive skin, the overall tolerability of CRCNC was very good, which should help to ensure good adherence.

Up to three-quarters of subjects with rosacea experience ocular symptoms, which are potentially serious.[2,15] In this study, only three subjects reported ocular itching, a possible symptom of ocular rosacea,[2] at baseline, which is lower than what might be expected. On Day 22, no subject reported ocular itching. The number of subjects with ocular manifestations is too small to perform meaningful statistical comparisons or to draw clear conclusions.

While these results suggest that CRCNC is effective and well-tolerated, each of the studies was single-center in nature. Moreover, there was no control group, although subjects acted as their own control. Arguably, this might make the results at least as robust as those achieved via a comparison with another group. Nevertheless, the studies could and perhaps should be replicated in a larger, more diverse sample that includes a greater proportion of men, various skin types, and people from various ethnicities.

CONCLUSION

The two studies in this paper show that CRCNC is suitable as part of the skincare regimens advocated by the ROSCO panel for subjects with rosacea. In healthy subjects presenting with dry skin on the forearms, a single application of CRCNC produced a statistically significant and clear moisturization effect that persisted for at least 24 hours. TEWL values also decreased up to eight hours, reflecting a long-lasting improvement of skin barrier function. These findings, suggestive of improved skin function, were confirmed by objective and patient-reported observations such as dryness and feelings of tension and comfort in the subjects with rosacea and sensitive skin. Taken together, these results show that CRCNC is an effective and well-

TABLE 6. Severity of dryness and tension assessed by subjects and dryness assessed by trained raters

PARAMETER	NONE	VERY SLIGHT	SLIGHT	MODERATE	STRONG	COUNTS >0	MEAN VALUE	*P* VALUE	
Dryness assessed by the trained rater									
Baseline	39.4%	21.2%	27.3%	12.1%	0.0%	60.6%	0.6	n/a	
Day 22	60.6%	18.2%	15.2%	6.1%	0.0%	39.4%	0.4	0.001	
PARAMETER	**NONE**	**VERY SLIGHT**	**SLIGHT**	**MODERATE**	**STRONG**	**COUNTS >0**	**MEAN VALUE**	***P* VALUE VERSUS**	
								Basline	**Day 1, 30mins PA**
Tension assessed by subjects									
Baseline	39.4%	6.1%	30.3%	24.2%	0.0%	60.6%	0.8	n/a	n/a
Day 1, 30 minutes PA	90.9%	3.0%	3.0%	0.0%	0.0%	6.1%	0.0	<0.001	n/a
Day 22	75.8%	9.1%	9.1%	0.0%	6.1%	24.2%	0.3	0.003	0.109
PARAMETER	**NONE**	**VERY SLIGHT**	**SLIGHT**	**MODERATE**	**STRONG**	**COUNTS >0**	**MEAN VALUE**	***P* VALUE VERSUS**	
								Basline	**Day 1, 30mins PA**
Dryness assessed by subjects									
Baseline	30.3%	9.1%	39.4%	18.2%	3.0%	69.7%	0.9	n/a	n/a
Day 1, 30 minutes PA	97.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0	<0.001	n/a
Day 22	81.8%	6.1%	6.1%	0.0%	6.1%	18.2%	0.3	<0.001	0.063

Scale: 0=none, 0.5=very slight, 1=slight, 2=moderate, 3=strong; PA: postapplication; n/a: not applicable

tolerated moisturizer that improves hydration, cutaneous barrier function, and the visible appearance of sensitive rosacea skin.

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REFERENCES

1. Gallo RL, Granstein RD, Kang S, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol.* 2017;78(1):148–155.
2. van Zuuren EJ. Rosacea. *N Engl J Med.* 2017;377(18):1754–1764.
3. Blount B, Pelletier A. Rosacea: a common, yet commonly overlooked, condition. *Am Fam Physician.* 2002;66:435–440.
4. Moustafa F, Lewallen RS, Feldman SR. The psychological impact of rosacea and the influence of current management options. *J Am Acad Dermatol.* 2014;71(5):973–980.
5. Bewley A, Fowler J, Schöfer H, et al. Erythema of rosacea impairs health-related quality of life: results of a meta-analysis. *Dermatol Ther (Heidelb).* 2016;6(2):237–247.
6. van der Linden MM, van Rappard DC, Daams JG, et al. Health-related quality of life in patients with cutaneous rosacea: a systematic review. *Acta Derm Venereol.* 2015;95(4):395–400.
7. Gallo RL, Granstein RD, Kang S, et al. Rosacea comorbidities and future research: the 2017 update by the National Rosacea Society Expert Committee. *J Am Acad Dermatol.* 2017;78(1): 167–170.
8. Tan J, Almeida L, Bewley A, et al. Updating the diagnosis, classification and assessment of rosacea: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2016;176(2):431–438.
9. Spoendlin J, Karatas G, Furlano RI, et al. Rosacea in patients with ulcerative colitis and Crohn's disease: a population-based case-control study. *Inflamm Bowel Dis.* 2016;22(3):680–687.
10. Schaller M, Almeida LMC, Bewley A, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. *Br J Dermatol.* 2017;176(2):465–471.
11. Draelos ZD, Ertel K, Berge C. Niacinamide-containing facial moisturizer improves skin barrier and benefits subjects with rosacea. *Cutis.* 2005;76(2):135–141.
12. Matsui M, Pelle E, Dong K, Pernodet N. Biological rhythms in the skin. *Int J Mol Sci.* 2016;17(6):E801.
13. Pinnagoda J, Tupkek RA, Agner T, Serup J. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis.* 1990;22(3): 164–178.
14. Del Rosso JQ, Thiboutot D, Gallo R, et al. Consensus recommendations from the American Acne & Rosacea Society on the management of rosacea, part 1: a status report on the disease state, general measures, and adjunctive skin care. *Cutis.* 2013;92(5):234–240.
15. Wladis EJ, Adam AP. Treatment of ocular rosacea. *Surv Ophthalmol.* 2017;63(3):340–346.
16. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health Serv Insights.* 2013;6:61–68.

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