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# An International Evaluation of a Ceramide-Containing Hydrating Cleanser and Moisturizing Cream for the Improvement of Diabetes Mellitus-Related Xerosis

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## ABSTRACT

**Background:** Diabetes mellitus (DM) is a common disease. Seventy percent of patients present with a cutaneous complication, including xerosis. Ceramides-containing (CER) skincare promotes a healthy skin barrier. This international, multicenter, open-label cohort study evaluated twice-daily application for 1 month of CER-containing cleanser and moisturizing cream to improve DM-related xerosis.

**Methods:** Patients between 18 and 75 years with DM-related xerosis at baseline were eligible. Study visits were on days -30 to 0 (screening), day 0 (baseline), and week 4 (end of study). Evaluations included the Global Aesthetic Improvement Scale (GAIS) and the physician and subject-scored Dry Skin Classification Scale (DSCS). Subject-scored measures of quality of life (QoL) and satisfaction scale with treatment outcomes and product features took place at the end of the study. Tolerance was assessed by monitoring adverse events (AEs).

**Results:** N = 528 subjects from 19 countries completed treatment, the majority having DM type 2 (82.6%). N = 519 (98.3%) met the primary endpoint criteria (GAIS). The CER-containing skincare regimen resulted in statistically significant improvements from baseline ($P<0.001$) in all parameters of the physician and subject DSCS scores. Patients reported QoL significantly improved by week 4 ($P<0.001$). At the end of the study, 99.6% (525) of subjects were satisfied with skincare outcomes and product features (99.4% [524]). No product-related AEs were reported during the study.

**Conclusion:** CER-containing cleanser and moisturizer were associated with statistically significant improvements in DM-associated xerosis, physician and subject scored severity, patient satisfaction, and improved QoL. The skincare regimen was well tolerated.

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## INTRODUCTION

Diabetes mellitus (DM) is a common and debilitating disease that affects the skin.[1-4] DM is a worldwide public health problem projected to affect 592 million people (10.1% of the world's population) by 2035.[1] Type 2 diabetes mellitus (DM2) comprises most cases of DM and is primarily the result of excess body weight and physical inactivity.[2] Between 30% and 70% of patients with DM will present with a DM-related cutaneous complication.[1-4] Despite the growing interest in DM-related dermatologic conditions, data are limited and mainly address diabetic foot syndrome and ulcers.[3] Dermatologic conditions linked with DM vary in severity and can be benign, deforming, or life-threatening.[1-4] Such skin conditions offer insight into patients' glycemic control and can be the first sign of DM in undiagnosed patients.[3,4] Cutaneous disorders associated with DM can cause pain and severely impact quality of life (QoL), including interpersonal relationships.[3] Recognition and management of these conditions are important in maximizing QoL and avoiding severe adverse effects (AEs).[3]

DM-related xerosis can be associated with pruritus, more often localized, although the pathogenesis is not fully understood.[3,4] However, in DM the underlying pathophysiology, course of disease, comorbidities, complications, and treatment predispose patients to pruritus.[3,4] A prospective cross-sectional study of 120 patients with DM demonstrated that skin xerosis was significantly more advanced in patients with pruritus than those without pruritus ($P<0.01$).[4] Pruritus is more likely in DM patients with xerosis or diabetic neuropathy.[3,4]

Ceramides (CERs) are essential physiologic lipids required to construct and maintain the epidermal barrier. CERs-containing skincare using cleansers and moisturizers has been beneficial for xerosis related to various skin conditions.[5-7] This study aimed to investigate the benefits of a CER-containing skincare regimen on clinical signs and QoL in patients with DM-related xerosis.

## MATERIALS AND METHODS

### Study Treatment

All included subjects received unblinded, currently marketed study products (CeraVe® Hydrating Cleanser and Moisturizing Cream, CeraVe US). Subjects were instructed to apply the cleanser and moisturizer twice a day to the areas of xerosis.

### Study Population

Men or women aged 18 to 75 years diagnosed with DM-related xerosis were enrolled. Excluded were subjects with a history of allergy, anaphylaxis, allergic contact dermatitis, or hypersensitivity to any ingredients in the CERs-containing cleanser and moisturizing cream. Further excluded were those with atopy and other skin disorders that may have affected assessments or results of using the study products.

### Study Visits and Assessments

The 3 study visits occurred as follows: screening (day -30 to 0), baseline (day 0), end of study (EOS) (day 28 ± 5 days). Visits 1 and 2 could be combined to occur on the same day. Table 1 shows the scales used for assessment and the scoring schedule. Physicians and subjects used the Dry Skin Classification Scale (DSCS) to score skin roughness or scaling, skin pruritus, pain, erythema, and fissures on a 5-point scale at baseline and at EOS.[8] The Global Aesthetic Improvement Scale (GAIS) was scored by the physicians at EOS. The subject scored QoL aspects at baseline and EOS. Subject satisfaction with treatment outcomes, skincare use, cleanser, and moisturizer performance was scored at EOS. Finally, safety was assessed by monitoring AEs during all study visits.

### Statistical Considerations

The intent-to-treat (ITT/safety) population comprised all properly enrolled subjects. The per-protocol (PP) analysis included all enrolled subjects who met all inclusion and exclusion criteria, received study products, completed all visits within the specified window, completed assessments, and had no significant protocol violations that would affect the treatment evaluation. Safety analysis was performed on the ITT population [N = 531].

Efficacy analyses were performed on the ITT and PP populations, with ITT as the primary population and PP supportive. The primary efficacy endpoint was the physician-assessed GAIS (the frequency of subjects having at least improved condition) at the EOS.

IBM SPSS Statistics was applied for statistical analysis. The data were assessed for parametric or nonparametric distribution. Scaled variables are displayed as means +/- SD, and categorical variables are indicated by frequency tables or cross-tabulations.

The Mann–Whitney U test or the chi-squared test was used to evaluate the quantitative variables. For all analyses, significance (*P*-value) was set to <0.05.

A post hoc power analysis was conducted using G*Power,[9-11] with N = 528, a small effect size set at 0.2, and an α error probability of 0.05, 2-tailed, which revealed a power (1 - β) of 0.99 in detecting statistically significant group differences (baseline vs day 28 +/- 5 days) in the DSCS, at the 0.05 level.

## RESULTS

Sixty-two sites in 19 countries within 6 continents (Asia, Africa, North America, South America, Europe, and Australia) participated in the study (Table 2). A total of 531 subjects completed the study. Three subjects were excluded from the analysis due to incorrect enrollment (ie, the subjects met at least one exclusion criteria at baseline). The final sample available for data analyses was N = 528.

The active data collection phase of the study required 326 days to be completed.

**TABLE 1.**

**Study Visits, Procedures, and Assessment Scales**

| Scorer | Type of Information/Scale | Items Scored | Score | Baseline Day 0 | End of study (Day 28 +/ - 5 days) |
|---|---|---|---|---|---|
| Physician and Subject | Dry Skin Classification Scale[5] | Rough and/or scaling, pruritus, pain, erythema, fissures | 5-point: 0=none to 4=severe | X | X |
| Physician | Global Aesthetic Improvement Scale | Improvement of skin condition | 7-point: 3=very much improved to -3 very much worse | -- | X |
| Physician | -- | Tolerance, observed adverse events | -- | X | X |
| Subject | Quality of Life Questionnaire# | Impact of the condition on personal, social, leisure, work, or study | 4-point: very much to not at all | X | X |
| Subject | Satisfaction Questionnaire | Product features, use, treatment results | 5-point: extremely satisfied to extremely dissatisfied | -- | X |
| Physician | Assessment of compliance | -- | -- | -- | X |

#Over the last week, how embarrassed or self-conscious have you been because of your skin?
Over the last week, how much has your skin affected any social or leisure activities?
Over the last week, has your skin prevented you from working or studying? Score: (very much, a lot, a little, not at all)

**TABLE 2.**

| List of Participating Countries | | |
|---|---|---|
| Australia | Mexico | Taiwan |
| Belgium | Morocco | Thailand |
| Brazil | Panama | Turkey |
| Canada | Romania | United Kingdom |
| Chile | Russia | United States |
| Greece | Spain | |
| Italy | Portugal | |

The average age of the included subjects was 57.8 years (SD: 12.3; Range: 18 to 75), with no statistical difference between the average age between male and females in the study ($P$>0.05).

**Diabetes Type**

The majority of subjects had a diagnosis of DM2 (82.6%) compared with DM1 (17.4%), and the relative ratio of DM1 and DM2 did not vary based on gender ($X^2 = 0.22$, $P$=0.64).

The most common areas with xerosis where the study skincare products were used included legs (~76%), feet (~58%), arms (~56%), and hands (~50%). The average number of affected areas per subject was 6.1 (SD: 3.3; Range: 1 to 16) (Table 3).

**Subject Compliance to Study Treatment**

Subjects reported being compliant with 91.60% of the study product applications. Over 80% (n = 441/528) of subjects reported being fully compliant with the twice-daily application regimen throughout the study duration. No AEs were reported to be possibly or probably related to the study products used for the duration of the study.

**The Primary Efficacy Endpoint Scores**

The physician-assessed GAIS scores at week 4 showed that 519 (98.3%) subjects met the primary efficacy endpoint (scoring at least an improved skin condition) (Figure 1). As per the GAIS scores, the global appearance of xerosis did not worsen in any subject.

**Physician Dry Skin Classification Scale Scores**

All parameters of the physician-scored DSCS significantly ($P$<0.001) improved from baseline to EOS (Table 4). From the physicians' DSCS scores, a post hoc analysis was done to show the percentage of subjects that presented with each of the parameters at baseline who had at least a 1-point improvement comparing baseline vs EOS (Figure 2A). Figure 2B shows the percentage of subjects with each parameter at baseline with 1-point up to 4-point improvement, no change, or scored worse at EOS.

**Subject Dry Skin Classification Scale Scores**

The post hoc analysis for subject DSCS scores showed that roughness/scaling, itchiness, pain, erythema, and fissure scores significantly ($P$<0.001) improved by week 4 (Table 5) for subjects that presented with each of the parameters at baseline. Figure 3A shows the percentage of subjects that presented with each of the parameters at baselines who had at least a 1-point

**TABLE 3.**

| Demographics of the Sample Population | | |
|---|---|---|
| **Parameter** | **Subgroup** | **Frequency** |
| Gender | Men | 201 (38.1%) |
| | Women | 327 (61.9%) |
| Diabetes | Type 1 | 92 (17.4%) |
| | Type 2 | 436 (82.6%) |
| Affected Area | Face | 125 (23.7%) |
| | Scalp | 39 (7.4%) |
| | Neck | 92 (17.4%) |
| | Decolletage | 65 (12.3%) |
| | Torso (front), Torso (back) | 114 (21.6%), 145 (27.5%) |
| | Arm (left), Arm (right) | 300 (56.8%), 298 (56.4%) |
| | Hand (left), Hand (right) | 265 (50.2%), 266 (50.4%) |
| | Axilla (left), Axilla (right) | 29 (5.5%), 34 (6.4%) |
| | Leg (left), Leg (right) | 400 (75.8%), 408 (77.3%) |
| | Buttocks | 51 (9.7%) |
| | Foot (left), Foot (right) | 311 (58.9%), 309 (58.5%) |
| Number of Affected Areas | 1-5 | 239 (45.3%) |
| | 6-10 | 238 (45.1%) |
| | 11-16 | 51 (9.6%) |

**FIGURE 1.** Physician Scored Global Aesthetic Improvement Scale (GAIS).

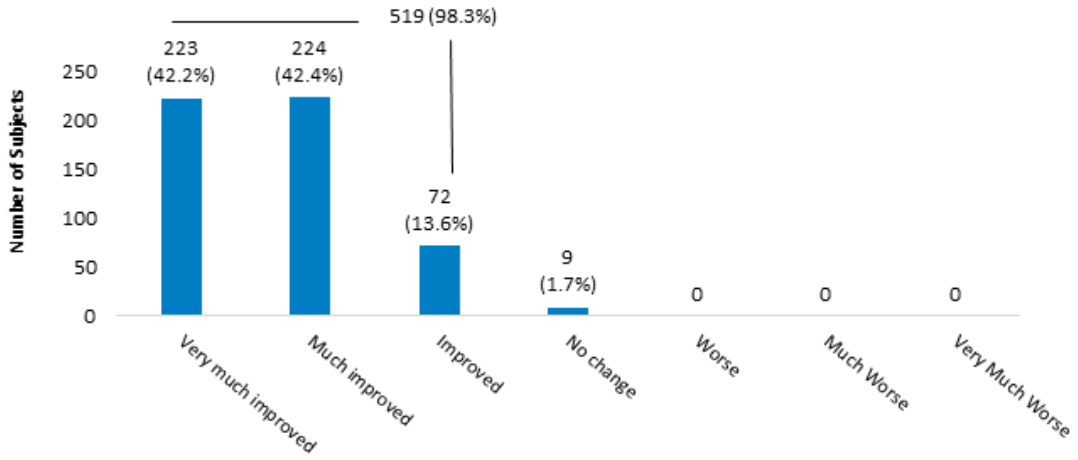
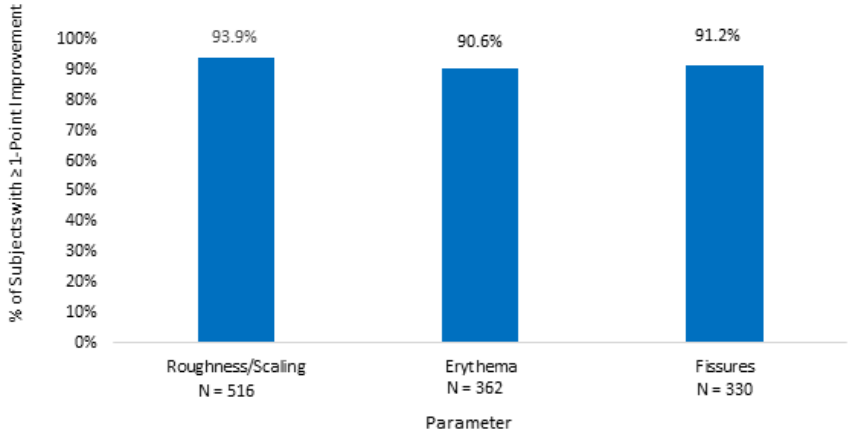



**FIGURE 2A.** Physician scored Dry Skin Classification Scale since baseline at week 4. Percentage of subjects with at least ≥1-point improvement (all statistically significant (*P*<0.0001).




improvement from baseline to EOS. Figure 3B further details the percentage of subjects with each parameter at baseline with 1-point up to 4-point improvement, no change, or scored worse at EOS.

**Subject Scored Quality of Life**

All three parameters of QoL scoring significantly (*P*<0.001) improved from baseline to EOS (Figure 4). At least one parameter of QoL improved in 400 (75.8%) subjects from baseline to EOS. Figure 5 shows the percentage of all subjects who had at least 1-point improvement in each of the 3 QoL parameters.

**Subject Scored Satisfaction With Treatment Outcomes and Product Features**

All 6 parameters of subject satisfaction scored highly (>80%) at week 4. On day 28, 99.6% (526) of subjects were satisfied with skincare outcomes (Figure 6). At EOS, 91.5% (483) of subjects said they would continue to use the CER-containing cleanser and moisturizer to improve their DM-related xerosis.

Three typical cases illustrate the results (Figures 7-9).

## DISCUSSION

The CER-containing cleanser and moisturizer were associated with significant (*P*<.0001) improvement in DM-related xerosis severity in 98% (519/528) of patients.

DM-related skin changes are a common complication seen in DM1 and DM2.[9] DM-related dermatologic conditions vary in severity and can, for example with those who have foot ulcers, lead to significant complications including amputations.[12,13]

In patients with DM, functional properties of the stratum corneum (SC) may be altered, impacting skin barrier function and leading to xerosis, pruritus, hyperkeratosis, and inflammation.[13] The status of the permeability and antimicrobial barrier of the skin in DM remains unknown.[12] In vivo impairment of the skin barrier (independent of the etiology) results from impairment of skin barrier homeostasis and decreases in epidermal proliferation and lipid synthesis.[14] In vivo and in vitro pre-clinical studies show that DM alters epidermis histology and suppresses the proliferation of keratinocytes.[15] Impaired keratinocyte homeostasis and epidermal barrier function are risk factors

**FIGURE 2B.** Physician scored percentage of subjects using Dry Skin Classification Scale since baseline at week 4.

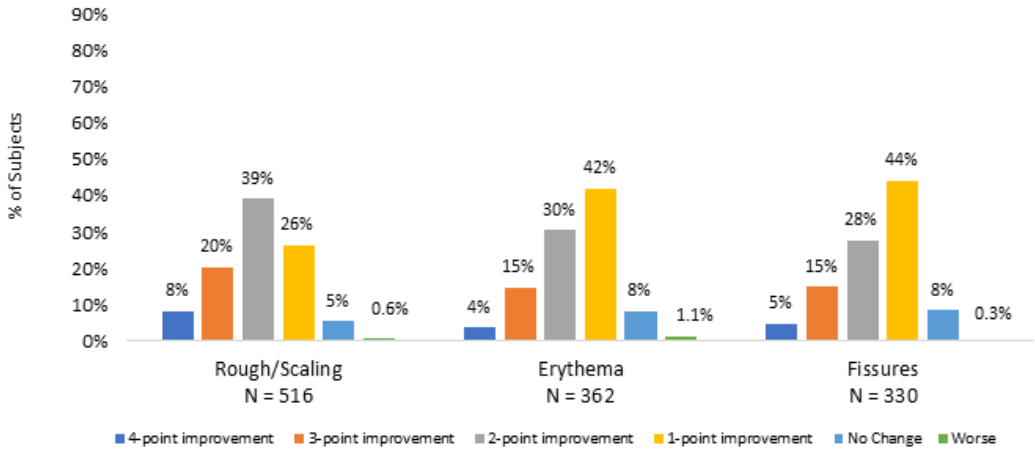



**FIGURE 3A.** Subject scored Dry Skin Classification Scale since baseline at week 4. Percentage of subjects with at least ≥1-point improvement (all statistically significant ($P$<0.0001).

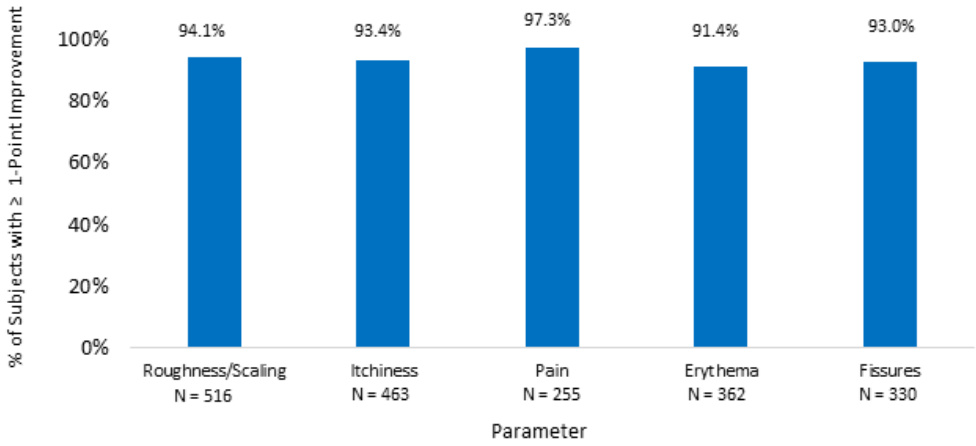



**FIGURE 3B.** Subject scored percentage of subjects using Dry Skin Classification Scale since baseline at week 4.

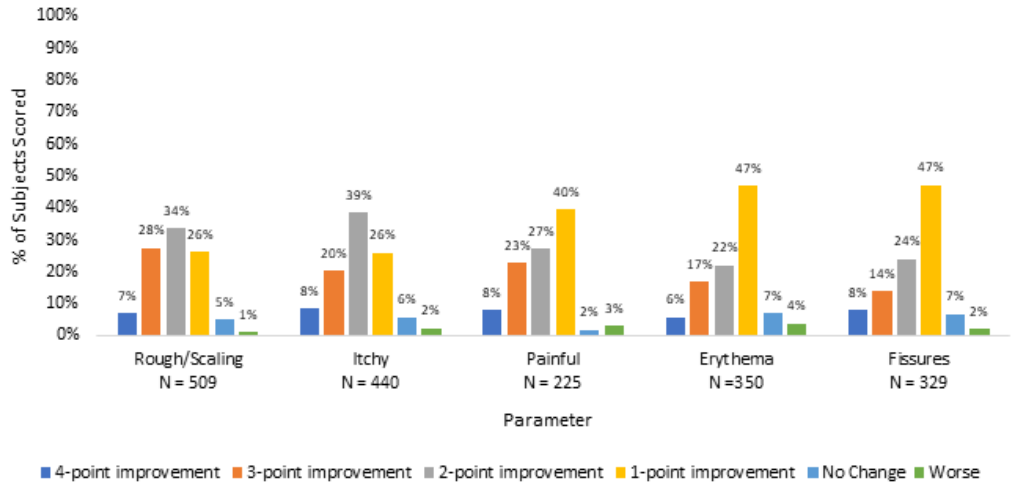
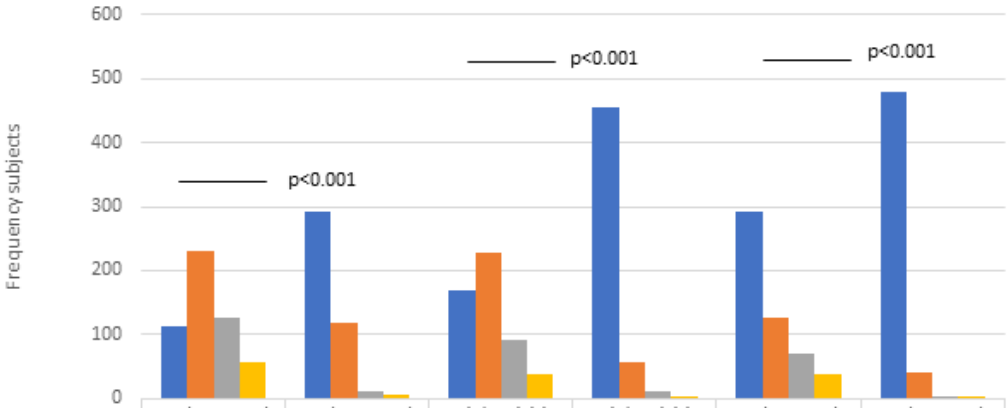


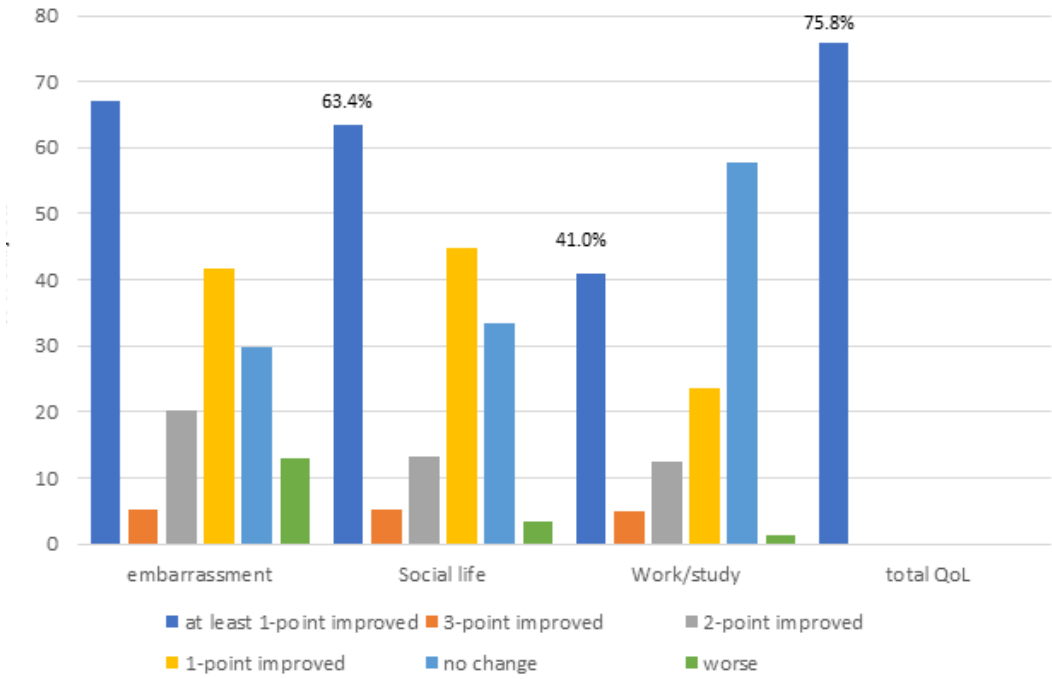
**FIGURE 4.** Subject self-assessed impact of xerosis on quality oflife baseline vs week 4 scores.




| | embarrassed baseline | embarrassed week 4 | social activities baseline | social activities week 4 | work or study baseline | work or study week 4 |
|---|---|---|---|---|---|---|
| not at all | 114 | 292 | 170 | 456 | 293 | 480 |
| a little | 231 | 118 | 228 | 57 | 126 | 41 |
| a lot | 125 | 11 | 91 | 12 | 71 | 3 |
| very much | 58 | 7 | 39 | 3 | 38 | 4 |

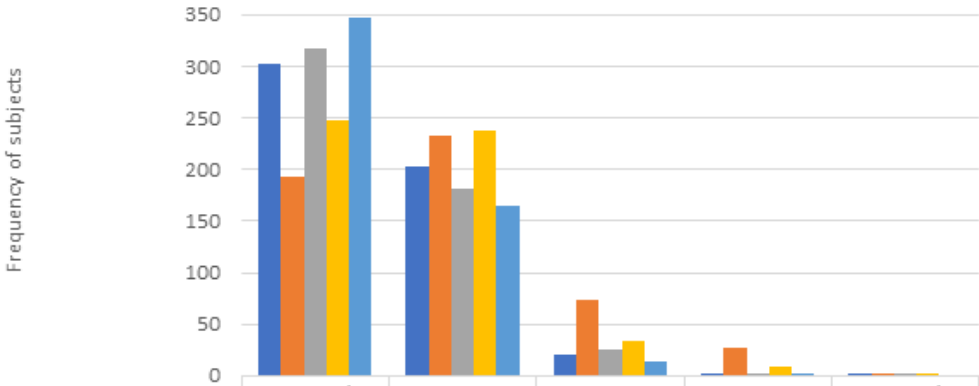
N=528
Questions listed in Table 1

**FIGURE 5.** Subject self-assessed impact of xerosis on quality of life point improvement scores at week 4.




N=528
Questions listed in Table 1.
Note: At least 1-point improvement includes all scores that had 1-point improvement and more. The rest of the scores shows the % of subjects that had 1 to 3-point improvement.

**FIGURE 6.** Subject scored satisfaction with the study products.




| | Extremely satisfied | Satisfied | Neutral | Dissatisfied | Extremely dissatisfied |
|---|---|---|---|---|---|
| Treatment outcomes | 302 | 203 | 21 | 1 | 1 |
| Regimen | 193 | 233 | 73 | 27 | 2 |
| Product features | 318 | 181 | 26 | 2 | 1 |
| Cleansing ability | 248 | 237 | 33 | 8 | 2 |
| Moisturizing ability | 347 | 165 | 14 | 1 | |

N = 528
Subject satisfaction questions:
Treatment outcomes: Overall level of satisfaction with product results
Treatment regimen: Overall level of satisfaction with the treatment regimen
Product features: Overall product features
My skin feels sufficiently clean after using the cleanser
My skin feels sufficiently moisturized after using the moisturizer

**FIGURE 7.** Typical case 1. (A) Left elbow – baseline. (B) Left elbow – day 28.

(A) (B)

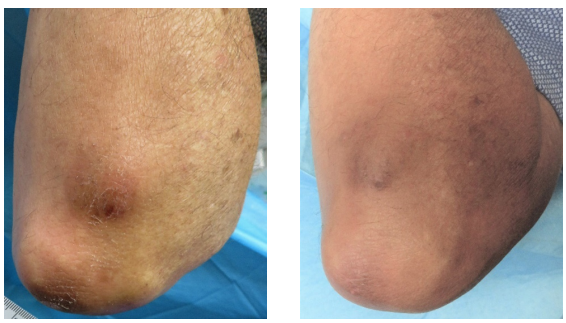
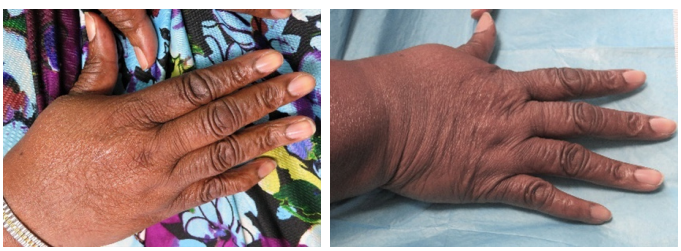


**FIGURE 8.** Typical case 2. (A) Right hand – baseline. (B) Right hand – day 28.

(A) (B)



for chronic wounds and infection.[12,13,16] Additionally, diabetic skin ages faster due to inflammation triggered by intrinsic and extrinsic factors.[17,18]

Gentle cleansers and moisturizers are recommended daily to restore and preserve skin barrier integrity in xerosis.[5-7,19,21-23,25] Skincare, specifically CER-containing skincare, was shown to improve the clinical signs and symptoms of AD, including pruritus, erythema, and fissuring.[7,6,24]

The pathogenesis of pruritus in DM is not fully understood, and various factors contribute to the development of this symptom.[4,12,26,27] Research suggests 2 main factors are associated with pruritus in DM: skin xerosis and diabetic polyneuropathy.[4,12,26,27] Skincare use has been shown to reduce DM-related pruritus significantly.[4] The present cohort showed that the CER-containing cleanser and moisturizer were associated with improvements in DM-associated xerosis severity and the reduction of pruritus.

**FIGURE 9.** Typical case 3. (A) Right heel – baseline. (B) Right heel – day 28.

(A) (B)

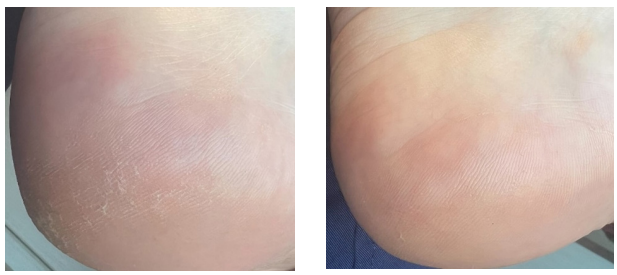


**TABLE 4.**

| Physician Scored Dry Skin Classification Scale | | | | | |
|---|---|---|---|---|---|
| 528 (100%) | Frequency (%) | Frequency (%) | Frequency (%) | Frequency (%) | Frequency (%) |
| Score | None (0) | Almost none (1) | Mild (2) | Moderate (3) | Severe (4) |
| Roughness/Scaling | | | | | |
| Baseline | 12 (2.3%) | 65 (12.0%) | 178 (33.7%) | 186 (35.2%) | 87 (16.4%) |
| Week 4 | 271 (51.0%) | 219 (42.0%) | 28 (5.3%) | 7 (1.3%) | 3 (0.5%) |
| Erythema | | | | | |
| Baseline | 166 (31.4%) | 141 (26.7%) | 106 (20.0%) | 83 (15.7%) | 32 (6.0%) |
| Week 4 | 409 (77.5%) | 93 (17.6%) | 19 (3.6%) | 6 (1.1%) | 1 (0.1%) |
| Fissures | | | | | |
| Baseline | 198 (37.5%) | 129 (24.4%) | 105 (19.9%) | 57 (10.8%) | 39 (7.4%) |
| Week 4 | 408 (77.3%) | 104 (19.7%) | 14 (2.6%) | 0 | 2 (0.4%) |

All parameters of the Physician Scored Dry Skin Classification Scale (roughness/scaling, erythema, fissures) significantly improved from baseline to the end of the study (week 4) ($P<0.001$)

**TABLE 5.**

| Subject Scored Dry Skin Classification Scale | | | | | |
|---|---|---|---|---|---|
| 528 (100%) | Frequency (%) | Frequency (%) | Frequency (%) | Frequency (%) | Frequency (%) |
| Score | None (0) | Almost none (1) | Mild (2) | Moderate (3) | Severe (4) |
| Roughness/Scaling | | | | | |
| Baseline | 19 (3.6%) | 75 (14.2 %) | 130 (24.6%) | 222 (42.0%) | 82 (15.5%) |
| Week 4 | 293 (55.5%) | 184 (34.8%) | 39 (7.4%) | 9 (1.3%) | 3 (0.5%) |
| Pruritus | | | | | |
| Baseline | 88 (16.7%) | 82 (15.5%) | 175 (33.1%) | 109 (20.6%) | 74 (14.0%) |
| Week 4 | 373 (70.6%) | 123 (23.3%) | 23 (4.3%) | 5 (1.0%) | 4 (0.8%) |
| Pain | | | | | |
| Baseline | 303 (57.4%) | 83 (15.7%) | 58 (11.0%) | 58 (11.0%) | 26 (4.9%) |
| Week 4 | 491 (93.0%) | 27 (0.5%) | 6 (1.1%) | 2 (0.4%) | 2 (0.4%) |
| Erythema | | | | | |
| Baseline | 178 (33.7%) | 160 (30.3%) | 77 (14.6%) | 72 (13.6%) | 41 (7.7%) |
| Week 4 | 426 (80.7%) | 79 (14.9%) | 14 (2.6%) | 6 (1.1%) | 3 (0.5%) |
| Fissures | | | | | |
| Baseline | 199 (37.7%) | 144 (27.3%) | 83 (15.7%) | 54 (10.2%) | 48 (9.0%) |
| Week 4 | 434 (82.2%) | 78 (14.8%) | 11 (2.1%) | 2 (0.4%) | 3 (0.5%) |

All 5 parameters of the Subject Dry Skin Classification Scale (roughness/scaling, itchiness, pain, erythema, fissures) significantly improved from baseline to the end of the study (week 4) ($P<0.001$)

### Limitations

This physician-initiated study has several limitations. For example, the study design did not include the evaluation of comparators. Instead, the CER-containing skincare products were evaluated in subjects with DM-related xerosis in a real-world setting. Therefore, the present findings may not extend to other CER-containing skincare products manufactured with different formulations. Moreover, subjects' medical management of DM was not monitored throughout the study.

## CONCLUSION

This international, multicenter, open-label cohort study showed that the CER-containing cleanser and moisturizer per physician and subject assessments were associated with statistically significant improvements in DM-associated xerosis, patient satisfaction with treatment outcomes, and improved QoL aspects. In addition, subjects reported high adherence to the skincare regimen. At EOS, 91.5% (483/528) of subjects indicated that they would continue to use the CER-containing cleanser and moisturizer to improve their DM-related xerosis.

## DISCLOSURES

The physician-initiated study was conducted according to the guidelines of the Declaration of Helsinki and, where applicable, approved by the local Institutional Review Boards in the participating countries. Informed consent was obtained following local rules and regulations before starting the study.

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