INTRODUCTION

Dry skin is characterized by symptoms that include an uncomfortable tightness, pain, itch, and tingling accompanied by discernible changes to the skin’s surface. We have developed a series of three face creams with a complex of skin-similar lipids arranged in an ordered lamellar structure designed to mimic the extracellular lipid layer surrounding the corneocytes in the stratum corneum. This study (RH02317/202496) was designed to assess the hydration potential of each lamellar moisturizer relative to a control (nonlamellar) moisturizer.

ORIGINAL CONTRIBUTION

Single application of lamellar moisturizers provides significantly increased hydration of the stratum corneum for up to 24 hours in a randomized trial

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Abstract

Background: Some moisturizing formulations can help restore and maintain the barrier function of the skin.

Objectives: This study was designed to assess the hydration potential of three lamellar moisturizers relative to a control (nonlamellar) moisturizer.

Methods: Healthy adults aged 18 to 65 years with self-reported sensitive skin, dry or very dry skin and Corneometry values of ≤40 a.u. on the lower legs, entered this randomized, evaluator-blind study. Products A and B together with a control product (Control X) were applied to one leg, while Product C and Control Y were applied to the other leg; with an untreated control site in both cases. The primary efficacy variable was the change from baseline in Corneometer assessments at 24 hours (Products A and B) or 12 hours (Product C) postapplication.

Results: At all timepoints (n = 30), Products A and B showed higher mean Corneometer readings compared to baseline and changes from baseline were statistically significant when compared to untreated sites. Higher mean readings relative to baseline were seen at sites treated with Control X (smaller magnitude than Product A and B) and with Product C. These changes were significant compared to the untreated site at 30 minutes and 2 hours (Control X), and at 30 minutes and 12 hours (Product C). Additionally, Control Y increased significantly at 12 hours.

Conclusion: A single application of a lamellar moisturizer significantly increased hydration of the stratum corneum for up to 24 hours (Products A and B) or 12 hours (Product C).

KEYWORDS
moisturizing, skin barrier
(nonlamellar) moisturizer. The test products were designated as Product A, Product B, and Product C. An earlier study (RH02222; protocol and informed consent form approved by the Freiburg Ethics Commission International) of Product B in 10 subjects demonstrated a sun protection factor (SPF) 20 (Figure 1). This study (RH02317/202496) followed International Organization for Standardization (ISO) 2444 guidelines. The protocol and informed consent form were approved by the Cardiff Independent Research Ethics Review Committee.

2 | PATIENTS AND METHODS

This was a randomized, evaluator-blind, intra-subject, single-use, complete block design study in healthy volunteers with self-reported sensitive skin that was also dry or very dry. Subjects were within the age range 18 to 65 years with skin type I to IV on the Fitzpatrick Skin Type Scale and Corneometry values of ≤40 a.u. on the lower legs. The study was conducted at Cutest Systems Ltd, Cardiff, Wales in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki. After providing written informed consent and being deemed eligible to participate in the study, participants entered a 5- to 7-day wash-out period. No use of shower gels, soaps, moisturizers, medicated washing/shower acne products, natural plants/herbs with or without fragrance, pain relief gels, or antioxidants was allowed on the lower legs except for the use of Simple® Soap during the wash-out period and for the duration of the study. Subjects were to refrain from leg hair removal for the same time period.

Poststudy product application there was to be no water contact to the legs and subjects were to avoid actions that could lead to the removal of test products, for example, crossing of legs. Any deliberate exposure of the test sites to natural sunlight, other sources of ultraviolet lights, or use of self-tanning products on the lower legs was prohibited. Subjects were to wear shorts or trousers that could be rolled up to the knee and sustained in this position throughout their stay at the clinic on testing days. Subjects were to refrain from exercising or drinking hot or cold caffeinated beverages within 2 hours (h) before each measurement timepoint. Subjects were also to refrain from swimming/using hot tubs or soaking their legs in any way.

A vertical line was drawn down the midpoint of the front of the leg, forming the edge of each test area. There were three test sites per leg in a vertical line, each measured 4 × 3 cm (width by height) positioned at least 3 cm from the ankle and knee. Sites were outlined using a skin marker pen. At least 1 cm between different application sites of the test products was assured to prevent them from spreading over. A standard amount (2 mg cm⁻²) was applied by a trained technician using an Eppendorf multi-pipette and spread over the test site with a finger protected with a disposable cot. The evaluator and other individuals involved with the conduct, analysis and reporting of clinical study data (not including dispensing staff) were blinded to study product allocations.

Products A and B together with a control product (Control X) were applied to one leg with an untreated control site designated Untreated J, while Product C and Control Y were applied to the other leg with an untreated control site designated Untreated K. The control product was applied to two different sites to act as the 24-h control (X) for Products A and B, and the 12-h control (Y) for Product C.

The primary efficacy variable was the change from baseline in Corneometer assessments at 24 hours (Products A and B) or 12 hours (Product C) postapplication which was individually compared between the treated sites and the untreated site using the Wilcoxon signed-rank tests. Other assessments were taken at 30 minutes (±5 minutes), 2 hours (±5 minutes), and 12 hours (±30 minutes) for Products A and B and 30 minutes (±5 minutes) for Product C. Hydration of the stratum corneum was measured using a Corneometer (Courage + Khazaka electronic GmbH, Germany). Skin conductance was also measured using a Skicon 200EX (Yayoi Co. Ltd, Japan). The Corneometer is based on capacitance measurement of the skin surface whereas the Skicon is based on the conductance of the same. Skin dryness was assessed at each test site at each timepoint by examiners using a five-point ranking scale as follows Table 1:

**FIGURE 1**  
RH02222 study—flow diagram

| Enrollment | Assessed for eligibility (n = 11) |
|------------|----------------------------------|
| Allocation | Received allocated intervention (n = 10) |
| Analysis   | PP population (n = 10)            |
|            | Excluded (n = 1)                  |
The sample size calculation assumed the standard deviation for change from baseline on Corneometry measurement was 6 a.u. based on previous data. Therefore, 30 subjects would provide >90% power to detect a difference of 5 a.u. between the treated and untreated areas at a two-sided 0.05 level of significance. The randomization schedule was generated by Cutest Systems Ltd using the random number function of Microsoft Excel.

Of the 38 subjects that were screened for the study, 30 entered the study on Day 1 and had study products applied. All subjects had evaluable measurements for all test sites at all timepoints and thus, composed the intent to treat (ITT) population Figure 2.

The change in Corneometry values from baseline to 30 minutes, 2, 12, and 24 hours postapplication was calculated for the study products and the untreated (control) site. A nonparametric two-sided exact Wilcoxon Signed Ranks Test procedure was used to compare baseline subtracted values (Products A and B versus the untreated site; Product C versus untreated site). Statistical analysis was carried out using Unistat for Windows version 6.0 in Excel overlay mode (www.unistat.com). A multiple comparison procedure was used following the Wilcoxon test. For the primary comparisons, Hochberg's procedure was used to assess the significance of treatment differences.

3 | RESULTS AND DISCUSSION

Both Product A and Product B showed higher mean Corneometer readings at all timepoints compared to baseline suggesting increased hydration. The changes from baseline were statistically significant at all times of assessment when compared to untreated sites. Higher mean readings were also seen at sites treated with Control X, but these were of a smaller magnitude compared to Products A and B. Statistical analysis indicated the changes seen with Control X were only significant versus the untreated site at 30 minutes and 2 hours. Higher mean Corneometer values were also noted at 30 minutes and 12 hours with Product C relative to baseline. These were statistically significant when compared to the untreated test site. A statistically significant increase was noted with Control Y at 12 hours, but this was of a smaller magnitude (Figure 3).

Products A and B both showed higher mean Skicon readings at all timepoints relative to baseline suggesting increased hydration. These changes were statistically significant compared to untreated skin except at 24 hours when only Product B was still significant. Higher mean Skicon readings were also seen at sites treated with Control X; however, these were of a smaller magnitude compared to Products A and B. Higher mean Skicon values were also noted at 30 minutes and 12 hours with Product C relative to baseline. An increase with Control Y was observed at 30 minutes but this was of a significantly smaller magnitude than Product C.

Products A, B, and C all showed lower mean skin dryness ratings at all timepoints compared to baseline indicating increased hydration. These changes were statistically significant compared to untreated skin. A decrease was also noted with Control X at 30 minutes, 2 and 12 hours and Control Y at 30 minutes.

The results of this single application study showed significant increase in hydration of the stratum corneum for up to 24 hours for Product A and Product B, and up to 12 hours for Product C. All products were generally well tolerated.

Following on these results, a clinical study to further assess the effect of Products A, B, and C on facial skin sensitivity and barrier function on the leg over 4 weeks was initiated (RH02321; protocol and informed consent form approved by the IntegReview Ethical Review Board, Austin, Texas). This single-center, examiner-blind, four-arm, randomized controlled parallel-group study compared Products A, B, and C to the same nonlamellar control (Control). There was a wash-out period of 2 to 3 days between screening and baseline visits, during which only Dove® Extra Sensitive Beauty bar could be used to cleanse mean readings were also seen at sites treated with Control X, but these were of a smaller magnitude compared to Products A and B. Statistical analysis indicated the changes seen with Control X were only significant versus the untreated site at 30 minutes and 2 hours. Higher mean Corneometer values were also noted at 30 minutes and 12 hours with Product C relative to baseline. These were statistically significant when compared to the untreated test site. A statistically significant increase was noted with Control Y at 12 hours, but this was of a smaller magnitude (Figure 3).

Products A and B both showed higher mean Skicon readings at all timepoints relative to baseline suggesting increased hydration. These changes were statistically significant compared to untreated skin except at 24 hours when only Product B was still significant. Higher mean Skicon readings were also seen at sites treated with Control X; however, these were of a smaller magnitude compared to Products A and B. Higher mean Skicon values were also noted at 30 minutes and 12 hours with Product C relative to baseline. An increase with Control Y was observed at 30 minutes but this was of a significantly smaller magnitude than Product C.

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the face and lower leg. It was planned to randomize 135 patients in order to enroll 120 patients (30 patients per group) in the study. During enrollment of patients, the study was cancelled by the sponsor: 122 patients were randomized and received at least one application of study product, thus deeming them appropriate for inclusion in the ITT study population (Figure 4). Subjects were 18 to 65 years of age.

**RH02321 study**

**Enrollment**

- Randomized (n = 122)

**Allocation**

- Received Product A (n = 31)
- Received Product B (n = 30)
- Received Product C (n = 30)
- Received control (n = 31)

**Follow-up**

- Discontinued
  - Sponsor decision n = 31
  - Adverse event n = 1
  - Requested withdrawal n = 1

- Discontinued
  - Sponsor decision n = 28
  - Requested withdrawal n = 0

- Discontinued
  - Sponsor decision n = 29
  - Requested withdrawal n = 1

**Analysis**

- ITT population (n = 31)
- ITT population (n = 30)
- ITT population (n = 30)
- ITT population (n = 31)

**Figure 3** Hydration data for untreated, control moisturizer, and lamellar moisturizer sites. Data are Corneometer readings presented as percent change from baseline.

**Figure 4** RH02321 study—flow diagram.
with skin type I to IV on the Fitzpatrick Skin Type Scale. While not statistically tested, the results of the study indicated that Products A, B, and C were effective in reducing facial skin sensitivity, providing moisture to the stratum corneum and enhancing/repairing skin barrier properties on both the face and leg. Additionally, Products A, B, and C were generally more effective than the Control in reducing facial skin sensitivity, providing moisture to the stratum corneum and enhancing/repairing skin barrier properties.

In general, Products A, B, and C were well tolerated by the subjects under the conditions of this study and for the duration of time that the subjects were treated before the study was discontinued. Of the 30 to 31 subjects per product group that were randomized and received at least one study product, only one subject in the Product A and B groups and three subjects in the Product C and Control groups had at least one adverse event (AE) that was determined to be possibly related to the test material. One subject each in the Product A and Control groups withdrew from the study as a result of an AE(s). The following skin and subcutaneous events were reported: papule, blister (one report each); erythema (two reports); acne, rash (three reports each). No serious AEs occurred during the study.

4 | CONCLUSION

These data demonstrate that a single application of a lamellar moisturizer significantly increases hydration of the stratum corneum for up to 24 hours (Products A and B) and 12 hours (Product C), whereas multiple applications of these lamellar moisturizers can show additional benefits such as reducing skin sensitivity and helping to repair the skin moisture barrier.

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CONFLICTS OF INTEREST

Stephanie Nisbet is an employee of GlaxoSmithKline Consumer Healthcare and holds GSK shares. Jane Snatchfold provides independent consulting services to GSK Consumer Healthcare.

AUTHOR CONTRIBUTIONS

All authors contributed to data analysis and interpretation and drafting this article. All authors approve the final version of the article and agree to be accountable for all aspects of the work.

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