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ORIGINAL ARTICLE

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Assessment of the Vehicle for Roflumilast Cream Compared With a Ceramide-Containing Moisturizing Cream in Mild Eczema

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ABSTRACT

Background: Inflammatory dermatologic conditions suitable for topical treatments benefit from a hydrating vehicle that improves the skin barrier without irritation.

Objective: This research was designed to assess skin barrier effects and aesthetic attributes of the vehicle for topical roflumilast cream (vehicle) vs a currently marketed ceramide-containing moisturizing cream (moisturizer).

Methods: This was a single-site, randomized, intraindividual, double-blind, controlled study conducted over 17 days. Patients (aged ≥18 years) with mild, symmetric asteatotic eczema of the lower extremities were enrolled to receive lower leg applications of the vehicle on one leg and moisturizer on the other. The primary efficacy endpoint was a change in transepidermal water loss (TEWL) from baseline to day 15. Secondary efficacy endpoints included change from baseline in TEWL at other study visits, change from baseline in hydration as assessed via corneometry, and patient- and investigator-rated assessments of the products. Safety and tolerability were also assessed.

Results: A total of 40 patients enrolled in the study. The primary efficacy endpoint was met for both treatments. A statistically significant difference in TEWL on day 1 favored the moisturizer, but no difference was seen between vehicle and moisturizer at any other timepoint. Both vehicle and moisturizer also met the secondary efficacy endpoint of change from baseline in hydration.

Limitations: The sample size was small.

Conclusions: The vehicle for roflumilast cream performed similarly to a leading, currently marketed, dermatologist-recommended, ceramide-containing moisturizer across all patient- and investigator-rated assessments of efficacy, tolerability, and aesthetic properties in patients with mild asteatotic eczema.

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INTRODUCTION

The role of the vehicle in topical prescription treatments is to deliver therapeutic concentrations of an active drug to a designated skin target site to support patient adherence and satisfaction, ideally without skin irritation. To achieve a pharmacological effect, the drug must be able to penetrate through the stratum corneum (SC) into the viable epidermis and dermis. The skin barrier is composed of terminally differentiated keratinocyte cells (corneocytes) and lipid lamellae, which prevent the movement of water out of the skin.[1,2] Most topical prescription treatments use penetration enhancers, such as propylene glycol, polyethylene glycol, and ethanol, to overcome the barrier properties of the skin by intentionally disrupting lipids in the SC to enhance drug permeability, inducing skin irritation.[2,3] For example, ruxolitinib, crisaborole, pimecrolimus, and tapinarof creams contain propylene glycol, mupirocin ointment contains polyethylene glycol, and clobetasol propionate spray contains ethanol.[4-9] While they are useful for increasing drug penetration and enhancing drug delivery, these vehicles can also inhibit epidermal repair and contribute to local tolerability issues.[10,11]

Skin barrier dysfunction is present in atopic dermatitis (AD) and other inflammatory skin diseases, resulting in water loss, penetration of irritants and allergens, and skin microbiome disruption.[12] The defective skin barrier of patients with AD is worsened by penetration enhancers, possibly delaying disease resolution. Patients who use topical prescription medications for AD frequently experience exacerbation of stinging, itching, and burning.[13] Ideally, these unwanted side effects should be minimized while optimizing topical drug absorption and limiting systemic drug absorption. This highlights the need for prescription topical formulations that maintain and repair the skin barrier function without the use of irritating or sensitizing excipients.[14] The effect of a formulation on the skin barrier can be assessed through noninvasive assessments, such as

transepidermal water loss (TEWL) and corneometry. TEWL is a measurement of water vapor leaving the skin, which increases with skin barrier damage and decreases with skin barrier repair.[15] Corneometry assesses the amount of water in the skin based on an indirect electrical measurement of skin water content.[16]

Roflumilast is a selective and highly potent phosphodiesterase 4 inhibitor.[17] Roflumilast cream 0.3% was recently approved by the US Food and Drug Administration (FDA) to treat chronic plaque psoriasis (July 29, 2022).[18,19] Topical roflumilast is being investigated for the treatment of several other dermatological conditions, including scalp psoriasis, seborrheic dermatitis, and AD.[20,21] The vehicle for topical roflumilast cream is water-based and formulated at physiological skin pH (5.5), without propylene glycol, polyethylene glycol, ethanol, or fragrances. Excipients include an emollient emulsifier that does not extract epidermal lipids at body temperature and temperatures safe for the skin[22] and has not been used in any FDA-approved prescription topical product previously. This research compared the vehicle for topical roflumilast cream (vehicle) with a currently marketed, dermatologist-recommended ceramide-containing cream (moisturizer) in patients with mild lower extremity asteatotic eczema using patient, dermatologist/investigator, and noninvasive skin barrier assessments.

MATERIALS AND METHODS

Study Design

This was a single-site, randomized, double-blind, controlled, 17-day split-body study. All patients signed an informed consent form before any study activities (Allendale Institutional Review Board, Old Lyme, CT).

Study Population

Forty male and female adults (≥18 years of age) with mild, symmetric asteatotic eczema of the lower extremities were enrolled. Key exclusion criteria were any dermatological disorder that, in the investigator's opinion, may interfere with the accurate evaluation of the study condition of mild eczema; significant excoriation; not willing to use the same self-selected cleanser during the study; use of any topical prescription or over-the-counter medicated products to the legs for 2 weeks before study entry; clinically significant unstable medical disorders; history of a psychological illness or condition that would interfere with their ability to understand and follow the requirements of the study; or currently participating in any other clinical trial.

Treatments

Patients were randomized as to which leg received applications of vehicle or moisturizer. No topical medications of any kind, other than the study product, could be used on the hands or legs during the study. Before treatment application on study day 1, patients underwent TEWL measurement at a predetermined target site 6 inches above the ankle on the mid-anterior shin on both legs for 1 minute. After the TEWL measurement, the investigator took the average of 3-pin probe corneometry measurements on the right and left anterior shin slightly to the side of the TEWL measurement site. Research center staff then applied the assigned blinded study products to patients' lower legs from knee to ankle. Staff changed gloves between each study product application.

On days 2 to 5 and on day 15, all product applications occurred at the research center under the direction of the research staff. On day 5, patients received a study diary and the study products in 2 jars labeled "left leg" and "right leg." Patients applied the randomized assigned product to the corresponding lower leg every morning on days 6 through 14. After the second visit on day 15 and until day 17 assessments, patients were asked to stop applying any moisturizer to their legs but continue with their usual bathing products and routine.

Study Assessments

On days 1, 2, 3, 4, 5, 15, and the morning of day 17, patients returned to the research center at least 4 hours after product application for TEWL and triplicate pin probe corneometry measurements from both legs, investigator assessments, and patient assessments.

The investigator assessments, conducted prior to product application, included measurements of erythema, desquamation, roughness, and dryness (scale: 0=none; 4=severe). A local tolerability assessment of skin irritation using the Berger and Bowman skin irritation score (scale: grade 0=no evidence of irritation; grade 7=strong reaction spreading beyond the test site) was also recorded.[23]

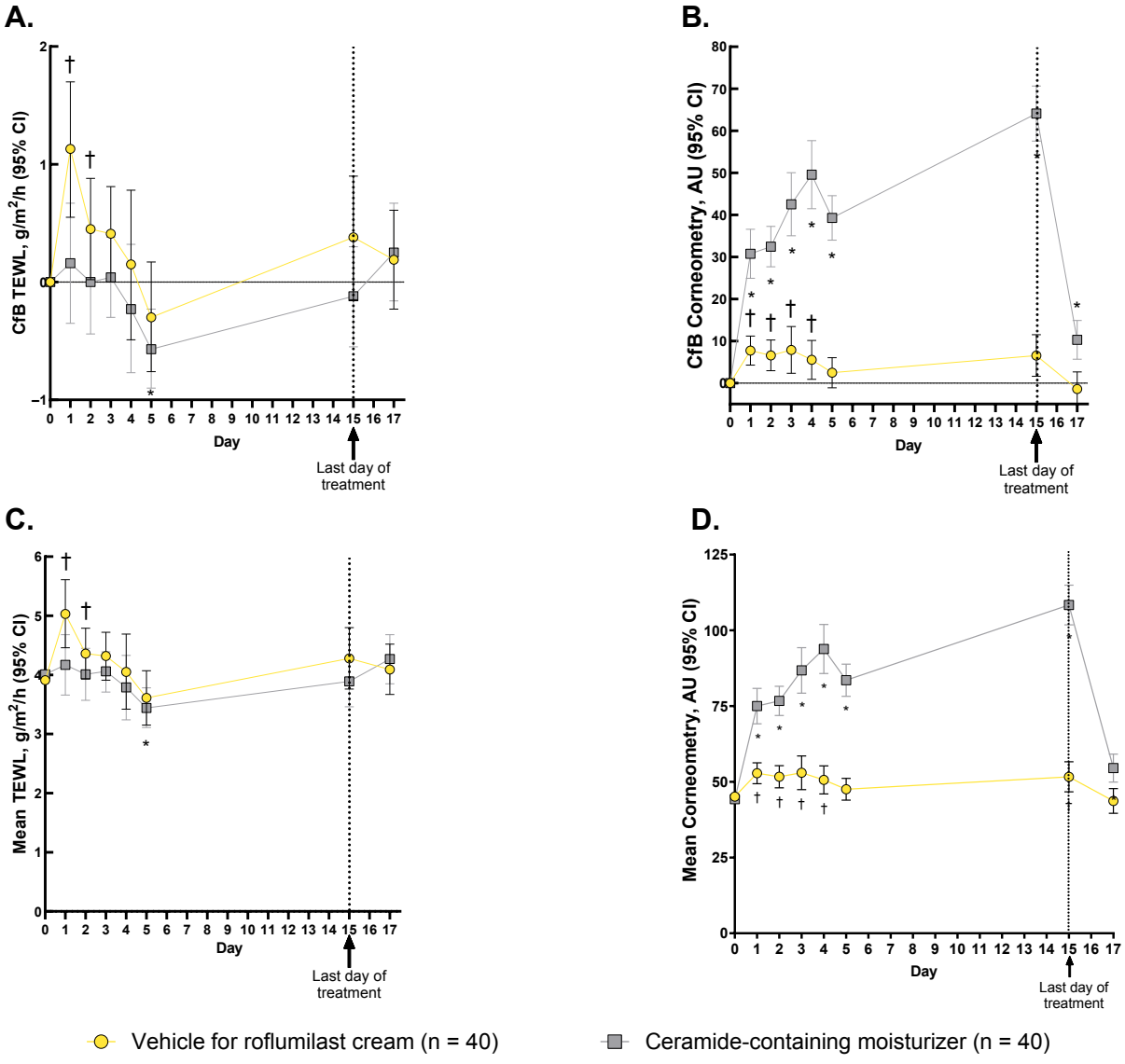
The patient assessments were performed 10 to 15 minutes after product application and included measurements of dryness, redness, roughness, tightness, irritation, moisturization, smoothness, and overall skin appearance (scale: 0=none; 4=severe). Additionally, patient-perceived noxious sensory stimuli assessments occurred 10 to 15 minutes after product application. Patients completed a product questionnaire on days 1 and 15 immediately after product application. On day 1, the product questionnaire contained 4 questions each rated on a 5-point scale (1=good; 5=poor):

1. How would you rate how the product spreads on your skin?
2. How would you rate how quickly the product absorbs into your skin?
3. How would you rate the feel of your skin after applying the product to your skin?
4. How would you rate the smell of the product after you apply the product to your skin?

The questionnaire on day 15 consisted of a single question answered on a 5-point scale (1=likely; 5=unlikely): if allowed to do so, how likely would you be to continue using this product to treat your dry skin?

The primary efficacy endpoint was the change in TEWL from baseline to day 15, indicating an improvement in skin barrier function. Secondary efficacy endpoints included change from baseline in TEWL at days 2, 3, 4, 5, 17, and improvement in skin hydration from baseline, as assessed via corneometry, at days 2, 3, 4, 5, 15, and 17. Noninvasive parametric data were analyzed using a 2-tailed paired t-test for the change from baseline in TEWL and corneometry assessments. Treatment comparisons of efficacy and patient assessments of treatment attributes were each assessed on an ordinal scale as nonparametric data analyzed with a Mann-Whitney test. Significance was set at a *P*-value less than or equal to *P*=0.05. Safety and tolerability were assessed as adverse events (AEs) and investigator and patient assessments of local tolerability.

FIGURE 1. Change from baseline in TEWL (A) change from baseline in corneometry (B) mean TEWL (C) and mean corneometry (D) measurements following application of moisturizer or roflumilast vehicle from days 1 to 15 and 2 days after last application (day 17).



AU, arbitrary units; CfB: change from baseline; CI, confidence interval; TEWL, transepidermal water loss.
*P<0.05 ceramide-containing moisturizer vs baseline.
†P<0.05 vehicle for roflumilast cream vs baseline.

RESULTS

All 40 (100%) patients successfully completed the study. The mean patient age was 52 years and 80% were female; 29 (72.5%) patients were categorized as having Fitzpatrick skin types I to III and the remaining 11 (27.5%) patients had Fitzpatrick skin types IV to VI.

The primary efficacy endpoint, change in TEWL from baseline to day 15, was met for both vehicle and moisturizer as there was no meaningful change in TEWL from baseline for either the vehicle or the moisturizer, thus indicating no skin barrier damage. A slight difference in TEWL between treatment groups, favoring moisturizer occurred on day 1 ($P<0.05$), but no statistically significant difference between the vehicle and moisturizer was observed at all remaining timepoints including day 15 (Figure 1). No statistically significant change from baseline in TEWL was found at day 15 or in the 48 hours after discontinuation of product application, known as the regression period, for either treatment. During this time, TEWL decreased by 9.8% for vehicles and increased by 4.4% for moisturizer.

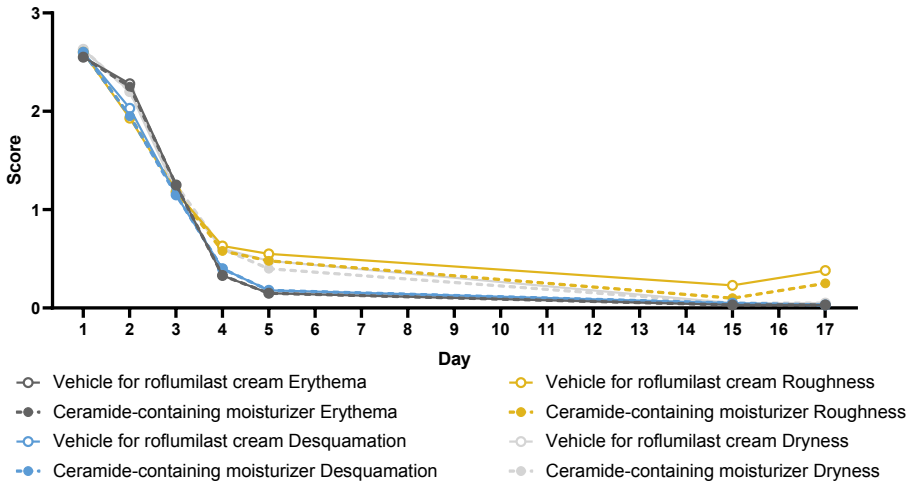
The secondary endpoint of change from baseline in corneometry values was met for the vehicle, with values maintained from day 1 to 4 and day 15; although these values were lower than those observed for moisturizer (Figure 1). After discontinuation of application, hydration values for both treatment groups were maintained compared with baseline; however, during the regression period, skin water content decreased more for moisturizer than vehicle.

Statistically significant and sustained improvements were observed for investigator-assessed erythema, desquamation, roughness, and dryness at all timepoints for both vehicle and moisturizer; both treatments had similar results at all timepoints (Figure 2). Statistically significant improvements also occurred with both treatments in patient-assessed measures of dryness, redness, roughness, tightness, irritation, moisturization, smoothness, and overall skin appearance with no statistically significant differences between treatments at any timepoint (Figure 3). On day 17, both treatments maintained similar improvements on both investigator and patient assessments after the 48-hour regression period, even though no product was applied.

Patient perceptions of moisturizer and vehicle were almost identical, with 100% of patients reporting that both treatments spread easily or somewhat easily and 97.5% of patients reporting that the treatment was quick to absorb or somewhat quick to absorb. The percentage of patients who reported the feeling of their skin was good or somewhat good after applying vehicle (85%) was comparable with moisturizer (82.5%). Most patients rated the smell of both products as neutral (neither good nor poor), somewhat good, or good. On day 15, most patients reported they would be likely or somewhat likely to continue using the moisturizer (95%) and vehicle (83%) to treat their dry skin if allowed to do so.

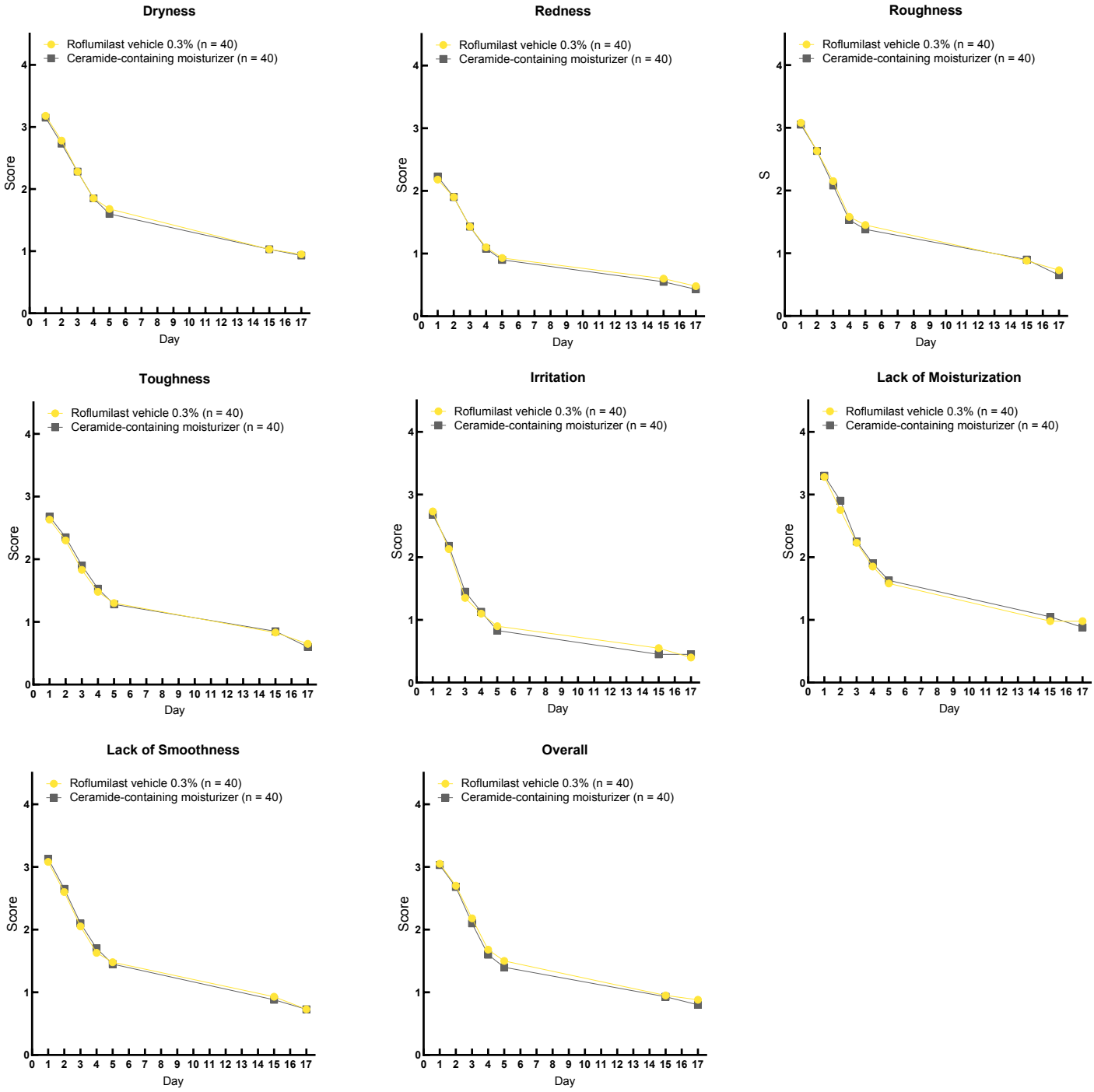
No AEs or local tolerability issues were reported by the patients, including no stinging or burning, for either treatment.

FIGURE 2. Investigator assessment of efficacy.



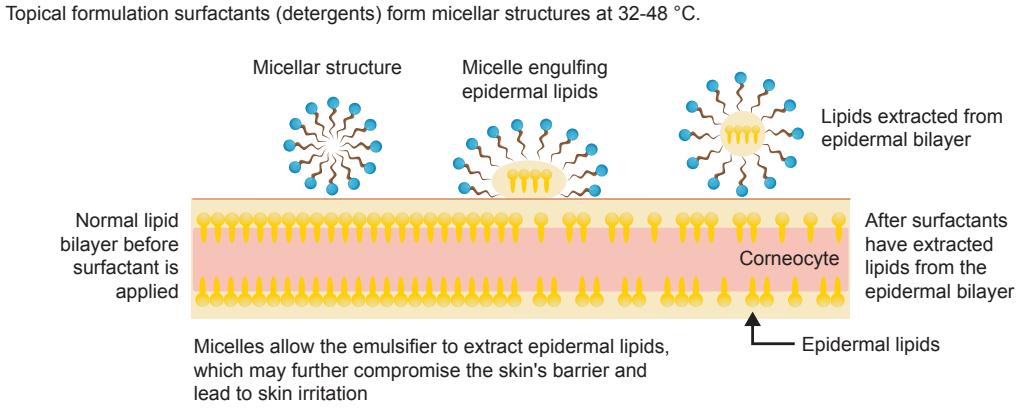
Each measure is evaluated on a 5-point ordinal scale (0=none; 4=severe).
For all any investigator efficacy assessments, no statistically significant differences were found between ceramide-containing moisturizer and roflumilast cream vehicle at any timepoint.

FIGURE 3. Patient assessment of efficacy.



Each measure is evaluated on a 5-point ordinal scale (0=none; 4=severe).
For all patient efficacy assessments, differences between ceramide-containing moisturizer and roflumilast cream vehicle were not significant at any timepoint.

FIGURE 4. Micellar lipid extraction process.



DISCUSSION

Many advances have been made in cosmetic formulation science based on new ingredient technologies that allow superior skin moisturization and aesthetics. Unfortunately, many of these advances have not been incorporated into prescription topical dermatologic formulations. Roflumilast cream is the first topical pharmaceutical to receive approval from the FDA that incorporates a new emulsifier, Crodafos CES (Croda Inc., Princeton, NJ), into its vehicle. This new emulsifier allows the water- and oil-based ingredients to be miscible without emulsifying skin barrier lipids in the SC. It also improves the aesthetics of the product by avoiding greasy residue. In clinical trials, the emulsifier allowed roflumilast to enter the skin, providing excellent efficacy.[18,20,21,24,25]

Topical roflumilast is formulated as a water-based cream with a novel mild emulsifier at the physiologic pH of the skin without the use of irritating excipients or fragrances. Roflumilast possesses a low molecular weight (403.2 g/mol), is lipophilic (LogP = 3.53), is water insoluble (solubility = 0.52–0.56 mg/L at 22°C), and has an affinity for protein. These properties of the roflumilast molecule support passive diffusion into the lipid-rich SC without the need for a penetration enhancer, such as propylene glycol, to disorganize the epidermal lipid bilayer to induce drug delivery when applying the topical formulation of roflumilast.[26] For example, when propylene glycol is combined with oleic acid or oleyl alcohol, such as in topical pimecrolimus cream, the skin barrier is dramatically compromised by fluidization and phase separation of intercellular lipids.[27] In contrast, the excipients used in the vehicle for topical roflumilast are intended to keep the active product dissolved, maintain the stability of the cream emulsion, and deliver a therapeutic concentration of roflumilast into the skin. Similarly, the solvent used to dissolve roflumilast in the vehicle, diethylene glycol monoethyl ether (DEGEE), maintains SC hydration unlike commonly used solvents such as propylene glycol, polyethylene glycol, and ethanol, which can modify the SC barrier or dry the skin.[28]

The Krafft temperature is the minimum temperature for a negatively charged emulsifier to dissolve oil into the interior of micelles. The oil-loving (hydrophobic) compartment at the core of the micelle rapidly captures lipids, while the water-loving (hydrophilic) headgroup region facing the micelle exterior keeps the oily contents solubilized in water (Figure 4). In most topical formulations, the formation of micelles allows the emulsifier to extract epidermal lipids, which may compromise the skin's barrier and induce skin irritation.[28,29] In contrast, roflumilast cream contains a blend of 2 negatively charged emulsifiers, cetearyl phosphate and ceteareth 10 phosphate (which are included in the Crodafos CES excipient), with high Krafft temperatures (>50°C).[22] Because of the high Krafft temperature of the emulsifiers used in roflumilast cream, micelles do not form at temperatures safe for the skin (<50°C), and thus roflumilast cream is incapable of extracting SC lipids,[22] thereby preserving the lamellar structure of the SC.

The characteristics of the excipients in the vehicle for topical roflumilast support the results observed for TEWL, hydration, and the investigator and patient assessments of efficacy. In this study of patients with asteatotic eczema, there was no change in TEWL during the study for either vehicle or moisturizer, indicating there was no damage to the skin barrier by either product. The improvement in skin moisturization was higher with moisturizer than with vehicle, which is not unexpected since a moisturizer is designed to increase skin hydration. Notably, corneometry values improved from day 1 to day 15 post-baseline with vehicle, indicating the skin also had better moisturization with this product. The results of this study suggest that a vehicle not only delivers the active ingredient but can also moisturize the skin.

In addition, vehicle aesthetics are an important consideration in topical medication formulation because they can impact patient adherence to therapy. Ointment vehicles are common in dermatologic topical treatments as they are the cheapest and

simplest to formulate, but the greasiness and propensity to transfer the medication to clothing and surfaces are problematic. Cream vehicles are aesthetically preferred by some patients; however, many formulations exist that may damage the skin barrier.[2,13]

Patient treatment compliance is an important consideration when selecting a prescription topical treatment for patients with chronic inflammatory skin diseases, such as AD, seborrheic dermatitis, and psoriasis. When patient satisfaction is low, compliance with the treatment regimen may be compromised.[30,31] In this research, the vehicle performed similarly to moisturizer in patient satisfaction, as measured by patient ratings of aesthetics such as spreadability, speed of absorption, feel of skin after application, and favorable smell. Most patients reported that they would like to continue applying both products at the end of the study.

CONCLUSION

In conclusion, this study demonstrates that the vehicle for topical roflumilast was comparable with a leading currently marketed, dermatologist-recommended, ceramide-containing moisturizer in terms of maintaining the skin barrier and aesthetic properties in patients with mild asteatotic eczema.

DISCLOSURES

ZDD received a research grant from Arcutis to contribute to the data presented in the paper. RCH, DWO, MSS, PB, and DRB are all employees of Arcutis Biotherapeutics, Inc.

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REFERENCES

1. Lemery E, Briançon S, Chevalier Y, et al. Surfactants have multi-fold effects on skin barrier function. *Eur J Dermatol.* 2015;25(5):424-435.
2. Danby SG, Draelos ZD, Gold LFS, et al. Vehicles for atopic dermatitis therapies: more than just a placebo. *J Dermatolog Treat.* 2022;33(2):685-698.
3. Lessmann H, Schnuch A, Geier J, et al. Skin-sensitizing and irritant properties of propylene glycol. *Contact Dermatitis.* 2005;53(5):247-259.
4. Incyte Corporation. OPZELURA™ (ruxolitinib) cream 1.5%. Available at: https://www.opzelura.com/. Published 2023. Accessed August 28, 2024.
5. GlaxoSmithKline. BACTROBAN (mupirocin) ointment 2%. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050591s034lbl.pdf. Published 2017. Accessed August 28, 2024.
6. Galderma Laboratories. CLOBEX (clobetasol propionate) spray 0.05%. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021835s006lbl.pdf. Published 2012. Accessed August 28, 2024.
7. Dermavant Sciences Inc. VTAMA (tapinarof) cream 1%. Available at: https://www.vtama.com/PI. Published 2022. Accessed August 28, 2024.
8. Novartis. ELIDEL (pimecrolimus) cream 1%. Available at: https://pi.bauschhealth.com/globalassets/BHC/PI/Elidel-PI.pdf Published 2020. Accessed August 28, 2024.
9. Pfizer. EUCRISA (crisaborole) 2% ointment. Available at: https://labeling.pfizer.com/ShowLabeling.aspx?id=5331. Published 2023. Accessed August 28, 2024.
10. Rhein LD, Schlossman M, O'Lenick A, et al. *Surfactants in Personal Care Products and Decorative Cosmetics.* 3 ed. Boca Raton, FL: CRC Press; 2007.
11. Del Rosso JQ, Kircik LH, Zeichner J, et al. The clinical relevance and therapeutic benefit of established active ingredients incorporated into advanced foam vehicles: vehicle characteristics can influence and improve patient outcomes. *J Drugs Dermatol.* 2019;18(2s):s100-s107.
12. Kim BE, Leung DYM. Significance of skin barrier dysfunction in atopic dermatitis. *Allergy Asthma Immunol Res.* 2018;10(3):207-215.
13. Silverberg JI, Nelson DB, Yosipovitch G. Addressing treatment challenges in atopic dermatitis with novel topical therapies. *J Dermatolog Treat.* 2016;27(6):568-576.
14. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol.* 2008;121(6):1337-1343.
15. Alexander H, Brown S, Danby S, et al. Research techniques made simple: transepidermal water loss measurement as a research tool. *J Invest Dermatol.* 2018;138(11):2295-2300.
16. Samadi A, Yazdanparast T, Shamsipour M, et al. Stratum corneum hydration in healthy adult humans according to the skin area, age and sex: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* 2022;36(10):1713-1721.
17. Dong C, Virtucio C, Zemska O, et al. Treatment of skin inflammation with benzoxaborole phosphodiesterase inhibitors: selectivity, cellular activity, and effect on cytokines associated with skin inflammation and skin architecture changes. *J Pharmacol Exp Ther.* 2016;358(3):413-422.
18. Lebwohl MG, Kircik LH, Moore AY, et al. Effect of roflumilast cream vs vehicle cream on chronic plaque psoriasis: the DERMIS-1 and DERMIS-2 randomized clinical trials. *JAMA.* 2022;328(11):1073-1084.
19. Arcutis Biotherapeutics Inc. Zoryve (roflumilast) cream 0.3%. Available at: https://www.arcutis.com/wp-content/uploads/USPI-roflumilast-cream.pdf. Published 2024. Accessed August 28, 2024
20. Gooderham MJ, Kircik LH, Zirwas M. The safety and efficacy of roflumilast cream 0.15% and 0.05% in atopic dermatitis: phase 2 proof-of-concept study. 29th European Academy of Dermatology and Venereology; October 29-31, 2020; Virtual.
21. Zirwas M, Draelos ZD, DuBois J, et al. Efficacy of roflumilast foam, 0.3%, in patients with seborrheic dermatitis: a double-blind, vehicle-controlled phase 2a randomized clinical trial. *JAMA Dermatol.* 2023;159(6):613-620.
22. Berk DR, Osborne DW. Krafft temperature of surfactants in vehicles for roflumilast and pimecrolimus cream and effects on skin tolerability. Society for Investigative Dermatology; May 18-22, 2022; Portland, OR.
23. Bowman JP, Berger RS, Mills OH, et al. The 21-day human cumulative irritation test can be reduced to 14 days without loss of sensitivity. *J Cosmet Sci.* 2003;54(5):443-449.
24. Lebwohl MG, Papp KA, Stein Gold L, et al. Trial of roflumilast cream for chronic plaque psoriasis. *N Engl J Med.* 2020;383(3):229-239.
25. Papp KA, Gooderham M, Droege M, et al. Roflumilast cream improves signs and symptoms of plaque psoriasis: results from a phase 1/2a randomized, controlled study. *J Drugs Dermatol.* 2020;19(8):734-740.
26. Trommer H, Neubert RH. Overcoming the stratum corneum: the modulation of skin penetration. A review. *Skin Pharmacol Physiol.* 2006;19(2):106-121.
27. Potts RO, Guy RH. Predicting skin permeability. *Pharm Res.* 1992;9(5):663-669.
28. Osborne DW, Musakhanian J. Skin penetration and permeation properties of Transcutol®—neat or diluted mixtures. *AAPS PharmSciTech.* 2018;19(8):3512-3533.
29. Froebe CL, Simion FA, Rhein LD, et al. Stratum corneum lipid removal by surfactants: relation to in vivo irritation. *Dermatologica.* 1990;181(4):277-283.
30. Finch T, Shim TN, Roberts L, et al. Treatment satisfaction among patients with moderate-to-severe psoriasis. *J Clin Aesthet Dermatol.* 2015;8(4):26-30.
31. Alinia H, Moradi Tuchayi S, Smith JA, et al. Long-term adherence to topical psoriasis treatment can be abysmal: a 1-year randomized intervention study using objective electronic adherence monitoring. *Br J Dermatol.* 2017;176(3):759-764.

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