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LETTER

Response to: Letter to the Editor Regarding "An Investigation of the Skin Barrier Restoring Effects of a Cream and Lotion Containing Ceramides in a Multi-Vesicular Emulsion in People with Dry, Eczema-Prone, Skin: The RESTORE Study Phase 1"

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Dear Editor,

We would like to respond to the points made by Dr Rawlings and Dr Lane in their Letter to the Editor regarding our paper entitled "An investigation of the skin barrier restoring effects of a cream and lotion containing ceramides in a multi-vesicular emulsion in people with dry, eczema-prone, skin: the RESTORE study phase 1".

Firstly, we thank the authors for their interest in our research and for providing this opportunity to discuss the findings further. Six points were raised which we will respond to in turn below.

1. The authors question the lack of traditional skin barrier measurements such as transepidermal water loss (TEWL). The manuscript clearly stated in the introduction that "Here we present the findings of the first study in a program of work…" and "The aim of this study was to determine the duration of SCH [stratum corneum hydration] imparted by the test products and compare it with current 'traditional' moisturisers…". The second study in the RESTORE program of research explores the skin barrier enhancing effects of a 28-day regimen using the test cream, and draws upon multiple techniques including, but not limited to, TEWL. The results of this second study are presented in a manuscript currently under review for publication.

    a. With respect to the wipe off measures suggested, we are familiar with the excellent work of Loden and colleagues quoted, and acknowledge the impact that residues left on the skin immediately after application can have [1, 2]. It is for this reason that we leave a longer than 2-h delay before taking the first measurement to ensure that the product is fully absorbed, and take the precaution of removing visible residues

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where still present using a dry wipe immediately prior to the 3-h time point. The study by Loden and Lindberg clearly shows that the effects of these residues are short-lived [2]. Whilst we recognise the different mechanisms of hydration mentioned, it was not our intention to discriminate between them.

b. The authors suggest that "The skin capacitance measures give the expected hydration improvements… due to the presence of glycerol in the products based upon its dielectric constant". It is correct that the corneometer is sensitive to salts, and humectants/emollients in products in addition to water. This means that corneometer readings from the sites treated with products containing these ingredients will indicate both the increase in stratum corneum water and the increase in salts and humectants/emollients. As Crowther concludes in his paper on the matter, skin moisturization is based upon multiple factors including an increase in salts and humectants/emollients, which are natural components of the skin necessary to hold onto water (moisture) [3]. Moreover, capacitance measurements directly correlate with clinical signs of dryness. Nevertheless, we share the authors' caution over corneometer measurements, and included visual skin dryness scoring in this study and have included additional measures of skin water content in our second study [4]. Notably, we found a direct correlation between corneometer readings and stratum corneum water content determined spectroscopically despite the potential interference from salts and humectants in the test products on corneometer measurements. What is striking is that the reference products in our study did not appreciably affect capacitance. The authors agree that such simple "paraffin-containing products give low capacitance measurements", suggesting that they do little to increase skin moisturization.

c. The authors appear to be suggesting that different products should be tested differently on the basis of the mechanism of hydration. We suggest that it is simply important to show which products impart greater increases in moisturization (irrespective of mechanism) because these products rightly or wrongly represent a single class of intervention (emollients according to the British National Formulary) for dry skin conditions.

2. We kindly acknowledge the authors' approval of our study cohort. The authors also offer an excellent study reference making use of the corneometer as a primary outcome measure, and supporting its use in cosmetic product claim substantiation with respect to skin moisturization [5]. They correctly identify that our corneometer readings taken at the 12-h measurement period after the single application of all of the products tested suggest that the skin is not moisturized enough to classify it as normal [hydrated] skin. This, we would like to point out, is consistent with the skin dryness scores we also presented in the manuscript. As we stated in the discussion, "The study is limited by its narrow focus on moisturization potential after a single application", and there is no reason to expect that a single application alone is sufficient to fully restore 'normal' skin moisturization. "Our intention is to follow this preliminary study with a vehicle-controlled trial investigating the effects of a treatment regimen with the TC [test cream] on skin barrier structure and function, in a similar population stratified by age." We are puzzled by the suggestion that "a sustained effect on skin hydration" can only be claimed if normal skin hydration is restored. We have been clear that the sustained effect is an 'increase in moisturization' and not restoration of hydration to a level considered normal. Moreover, the recent work by Draelos on the test lotion

provides evidence of the additive effect of regular applications over 4 weeks on skin dryness. It also shows that the effect is sustained for at least 48 h following cessation of treatment [6].

3. The authors are correct in their interpretation, which is consistent with our report.
4. The authors are right to correct the use of nomenclature in this manuscript. We inadvertently provided both the old and new nomenclature in different sections. For the avoidance of doubt the test products contained ceramide NP, ceramide AP, and ceramide EOP-S. The Draelos study demonstrates that stratum corneum ceramide levels are increased following 28 days of treatment with the test lotion [6]. As the authors highlight, stratum corneum lipid structure is a very important determinant of skin barrier function, which is why we have quantified the effects of the test cream on this property in our second study, the results of which are currently under review.
5. Whilst we provided evidence that the multivesicular emulsion (MVE) technology can control the release of a given substance, we were not able to provide such for glycerol or the skin lipids specifically. Accordingly, we have not specifically attributed the effects reported to this technology alone but instead to the formulation as a whole as appropriate, stating "…the combination of glycerol and skin lipids in a MVE vehicle significantly increase and prolong SCH compared to traditional emollients without these ingredients." As a study of a finished formulation, it is not possible to attribute the effects to a single ingredient.
6. Many factors must be considered when selecting a suitable reference product. Here we set out to evaluate a finished formulation (comprising multiple moisturizing ingredients and a unique delivery system) rather than a particular ingredient. Very little is left of the formulation when the moisturizing agents and emulsification/delivery system are removed. Simple paraffin emollients make a reasonable substitute for a vehicle in this case, but most importantly they represent the most widely prescribed competitor in the UK as explained in the manuscript.
    a. The authors offer evidence of the inferiority of the test products compared with another glycerol-containing but non-skin lipid/ceramide-containing product in the form of a single figure in a review article. The review provides no detail on which to assess the design and quality of the study and relies upon a single outcome, skin conductance. But as the authors have raised in their letter, such skin measurements alone are not a reliable measure of overall product performance.

In summary, we have faithfully reported the results of the study named above and specifically highlighted its limitations. We share the authors' view that multiple measures, including measures of skin barrier structure and function, are necessary to fully evaluate the performance of moisturizers. With this in mind we encourage you to read the results of the second and most comprehensive part of the RESTORE program of research when it is published.

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Compliance with Ethics Guidelines. This letter is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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