

## Appendix S1

# Supplementary Appendix

### *1 Clinical trial AtoCareOS: Skin Efficacy and Tolerability of a Cosmetic Product Combination Over 3 Months in Subjects With Atopic Eczema (NCT05790083)*

#### **1.1 Inclusion criteria**

- Written informed consent of the subject to participate in the study, or, in the case of children, consent of the parents/legal guardians to let their child participate in the study
- Willingness to actively participate in the study and to come to the scheduled visits or, in the case of children, willingness of the parents/legal guardians to actively support their child's participation in the study and to come to the scheduled visits with their child
- Female and/or male
- Approx. 50 % of study panel: children from 2 to 17 years of age
- Approx. 50 % of study panel: adult subjects between 18 and 75 years of age, preferably 20 of them between 60 and 75 years of age
- History of atopic dermatitis (AD), not necessarily acute lesions, but at least 2 flare-ups in the last winter season
- Dryness and erythema score each of at least 1 (according to proderm evaluation score, see page 13) over the body (trunk, arms and legs) diagnosed by a physician
- Itching assessed by the subjects or the subjects' parents/legal guardians on at least 2 days within 7 days prior to the start of the study
- Sub-panel: dryness score between 1 and 3, preferably of at least 2 (according to proderm evaluation score, see page 13) on lower legs

#### **1.2 Exclusion criteria**

- Female subjects (only of childbearing age): Pregnancy or lactation
- Drug addicts, alcoholics (only adults)
- AIDS, HIV-positive or infectious hepatitis
- Conditions which exclude a participation or might influence the test reaction/evaluation
- Participation or being in the waiting period after participation in cosmetic and/or pharmaceutical studies pertaining to the test area

- Cancer not being diagnosed as cured and requiring chemotherapy, irradiation and/or hormonal treatment within the last 2 years
- Insulin-dependent diabetes mellitus
- One of the following illnesses with reduced physical capability/fitness: asthma (symptom-free allergic asthma is not an exclusion criterion), hypertension, cardiovascular diseases
- Documented allergies to cosmetic products and/or ingredients, skin care and/or skin cleansing products as well as to ingredients of the test products
- Wounds, moles, tattoos, scars, irritated skin, excessive hair growth, etc. at the test area that could influence the investigation
- Systemic therapy with immuno-suppressive drugs (e.g. corticosteroids, cyclosporine, dupilumab) and/or antihistamines (e.g. antiallergics) within the last 7 days prior to the start of the study
- Systemic therapy with anti-phlogistic agents or analgetics (e.g. diclophenac, ibuprofen), except for minor pain relief medicine such as acetylsalicylic acid or paracetamol within the last 3 days prior to the start of the study
- Any topical medicinal products (e.g. topical corticosteroids, calcineurin inhibitors) at the test area within the last 5 days prior to the start of the study
- Any topical medication at the test area throughout the entire course of the study (except the medication normally used for treatment of atopic dermatitis)
- Known allergy to super glue (only sub-panel)

### **1.3 Study population**

The analyzed study population comprised N= 94 participants (mean age  $\pm$ SD: 27.7  $\pm$  20.8 years) including 43 children ( $\geq$ 2 years, mean age  $\pm$ SD: 8.9  $\pm$ 3.8 years) and 51 adults (mean age  $\pm$ SD: 43.6  $\pm$ 15.3 years). The male and female participants (21 male (22%), 73 female (78%)) had a history of AD with at least 2 flare-ups in the last winter season, but not necessarily presented with acute lesions at inclusion. Instrumental analysis of the skin barrier was only performed in a subpanel (N= 32) of the subjects (16 adults and 16 children) with very dry skin on the lower legs. Lipbarvis® sampling was only performed on adult subjects of the subpanel (N= 16).

### **1.4 Investigational cosmetic products**

The formulations of BNO 3732 and BNO 3731 are void of mineral oil, PEGs, microplastic, coloring, silicones or other purely occlusive agents. The intensive care product is formulated with the same ginger extract and CBD as compared to the body lotion, which additionally includes jojoba and castor oil. The product is solely marketed in Germany and recommended retail prices are 19.90 € in case of the body lotion (200 ml) and 26.90 € in case of the intensive care product (100 ml).’

## 1.5 Test schedule

|                                                                                                                                          | Day 1<br>(baseline) | Day<br>2 to 28 | Day<br>29       | Day<br>30 to 56 | Day<br>57       | Day<br>58 to 84 | Day<br>85       |
|------------------------------------------------------------------------------------------------------------------------------------------|---------------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| <b>Informed consent</b>                                                                                                                  | X                   |                |                 |                 |                 |                 |                 |
| <b>In-/Exclusion criteria</b>                                                                                                            | X                   |                |                 |                 |                 |                 |                 |
| <b>Prior/concomitant<br/>diagnosis and therapy</b>                                                                                       | X                   |                |                 |                 |                 |                 |                 |
| <b>Dermatological evaluation</b><br>(objective and vIGA-AD™)<br>(by a dermatologist or an<br>equally qualified physician)                | X                   |                | X               |                 | X               |                 | X               |
| <b>Acclimatisation</b> (30 min.) <sup>1)</sup>                                                                                           | X                   |                |                 |                 |                 |                 | X               |
| <b>TEWL</b> <sup>1)</sup>                                                                                                                | X <sup>2)</sup>     |                |                 |                 |                 |                 | X <sup>2)</sup> |
| <b>Lipbarvis® sampling</b> <sup>1)*</sup>                                                                                                | X                   |                |                 |                 |                 |                 | X               |
| <b>D-Squame® sampling</b> <sup>1)</sup>                                                                                                  | X <sup>2)</sup>     |                |                 |                 |                 |                 | X <sup>2)</sup> |
| <b>Questionnaire for RECAP</b><br>(by the subjects or the<br>subjects' parents/legal<br>guardians)                                       | X                   |                | X               |                 | X               |                 | X               |
| <b>Questionnaires for quality<br/>of life (DLQI/CDLQI/IDQOL)</b><br>(by the subjects or the<br>subjects' parents/legal<br>guardians)     | X                   |                | X               |                 | X               |                 | X               |
| <b>Application of test<br/>product(s)</b><br>(by the subjects or the<br>subjects' parents/legal<br>guardians on the subjects at<br>home) | X                   | X              | X <sup>4)</sup> | X               | X <sup>4)</sup> | X               |                 |
| <b>Questionnaire for product<br/>traits</b> (by the subjects or the<br>subjects' parents/legal<br>guardians)                             | X <sup>3)</sup>     |                | X               |                 | X               |                 | X               |

|                                                                                               |                         |  |   |  |   |  |   |
|-----------------------------------------------------------------------------------------------|-------------------------|--|---|--|---|--|---|
| <b>Diary</b> (by the subjects or the subjects' parents/legal guardians at home, twice weekly) | <div> X ←————→ X </div> |  |   |  |   |  |   |
| <b>Documentation of AEs/SAEs and changes in concomitant therapy</b>                           |                         |  | X |  | X |  | X |

1) Only in the sub-panel; if marked with “\*” only adult subjects of the sub-panel were tested (N=16)

2) For children: an attempt was made to perform all instrumental measurements. Especially with smaller children, it could not be guaranteed that all data could be collected completely.

3) At home, after first application of the test product(s).

4) The first application in the morning was performed after the visit.

## **1.6 Descriptive data analysis**

N, mean value and standard error of the mean (SEM) were given for raw data and calculated values. The mean values of raw data (with exception for the objective dermatological assessment) are presented as bar charts with SEM bars for all measurements and evaluations. For the objective dermatological assessment the mean values for all symptoms were presented as radar (spider) plot for visualization and mean values of selected parameters with relevant symptom burden at baseline (D1) were presented as bar charts with SEM bars in a separate diagram. For the determination of counts and proportions missing values and not applicable answers were excluded evident by adaptations in the given population sizes N.

Additionally to mean values, the proportion of “responders” in % was given for peak pruritus (based on NRS-11) for days 29, 57 and 85. Participants were defined as responders, if an improvement of at least 2 score points (defined as MCID) (1) compared to D1 was achieved at the respective assessment time (D29, D57, D85).

Complementary to the mean values of vIGA-AD<sup>TM</sup>, the proportion in % of participants achieving “vIGA-AD<sup>TM</sup> success” was determined for D29, D57 and D85. vIGA-AD<sup>TM</sup> success was defined as an improvement from score  $\geq 2$  at D1 by  $\geq 2$  points to vIGA-AD<sup>TM</sup> score of  $\leq 1$  at the respective assessment time (D29, D57, D85) (2-5).

For evaluation of product tolerability (“The test products are well tolerated.”) and satisfaction (“How satisfied are you with the test products?”) participants could state favorable (score 1 or 2 on a scale of 2,1,-1,-2) or unfavorable (score -1 or -2 on a scale of 2,1,-1,-2) towards the question/statement. For the analysis all favorable answers (score 1 and 2) were counted and the proportion in % were calculated for the respective population (N=92).

For the diary entries of flare-ups and corticosteroid use counts were calculated for the entire study. The proportions in % of participants with a sum  $\geq 1$  were calculated.

## **1.7 Statistical hypothesis testing**

A significance level of 0.05 (alpha) was chosen for statistical analysis. Due to the explorative character of this study, no adjustments for multiplicity was performed.

For mean peak pruritus based on NRS-11 two-sided paired Wilcoxon signed rank test and mean RECAP sum score and mean (C)DLQI sum score two-sided paired t-tests were performed for comparing each assessment time to the previous assessment time (D1, D29, D57, D85).

Furthermore, for objective dermatological evaluation, vIGA-AD<sup>TM</sup> and subjective dermatological evaluation, two-sided pairwise Wilcoxon signed rank tests were performed for each assessment time to the previous assessment time (D1, D29, D57, D85).

Pairwise comparisons of assessment times (D1, D85) were performed for instrumental measurements (*D-Squames*<sup>®</sup>, TEWL) for the complete subpanel (N=32, children and adults) with two-sided paired t-tests. For statistical testing of measurements (based on *Lipbarvis*<sup>®</sup>-sampling) only performed in the adult proportion (N=16) of the subpanel, also pairwise comparisons using paired two-tailed t-tests between assessment times (D1, D85) were performed.

## **1.8 List of used R-packages for statistical analysis:**

| package    | version | sources                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| base       | 4.1.3   | R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <a href="https://www.R-project.org/">https://www.R-project.org/</a> .                                                                                                                                                                                                                                                          |
| broom      | 1.0.5   | David Robinson, Alex Hayes and Simon Couch (2023). broom: Convert Statistical Objects into Tidy Tibbles. R package version 1.0.5. <a href="https://CRAN.R-project.org/package=broom">https://CRAN.R-project.org/package=broom</a>                                                                                                                                                                                                                                        |
| data.table | 1.14.8  | Tyson Barrett, Matt Dowle, Arun Srinivasan, Jan Gorecki, Michael Chirico and Toby Hocking (2024). data.table: Extension of `data.frame`. R package version 1.14.8. <a href="https://CRAN.R-project.org/package=data.table">https://CRAN.R-project.org/package=data.table</a>                                                                                                                                                                                             |
| extrafont  | 0.19    | Winston Chang (2023). extrafont: Tools for Using Fonts. R package version 0.19. <a href="https://CRAN.R-project.org/package=extrafont">https://CRAN.R-project.org/package=extrafont</a>                                                                                                                                                                                                                                                                                  |
| fmsb       | 0.7.5   | Minato Nakazawa (2023). fmsb: Functions for Medical Statistics Book with some Demographic Data. R package version 0.7.5. <a href="https://CRAN.R-project.org/package=fmsb">https://CRAN.R-project.org/package=fmsb</a>                                                                                                                                                                                                                                                   |
| ggbreak    | 0.1.2   | S Xu, M Chen, T Feng, L Zhan, L Zhou, G Yu. Use ggbreak to effectively utilize plotting space to deal with large datasets and outliers. <i>Frontiers in Genetics</i> . 2021, 12:774846. doi: 10.3389/fgene.2021.774846                                                                                                                                                                                                                                                   |
| ggplot2    | 3.4.4   | H. Wickham. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, 2016.                                                                                                                                                                                                                                                                                                                                                                                 |
| ggprism    | 1.0.4   | Charlotte Dawson (2022). ggprism: A 'ggplot2' Extension Inspired by 'GraphPad Prism'. R package version 1.0.4. <a href="https://CRAN.R-project.org/package=ggprism">https://CRAN.R-project.org/package=ggprism</a>                                                                                                                                                                                                                                                       |
| ggpubr     | 0.6.0   | Alboukadel Kassambara (2023). ggpubr: 'ggplot2' Based Publication Ready Plots. R package version 0.6.0. <a href="https://CRAN.R-project.org/package=ggpubr">https://CRAN.R-project.org/package=ggpubr</a>                                                                                                                                                                                                                                                                |
| haven      | 2.5.2   | Hadley Wickham, Evan Miller and Danny Smith (2023). haven: Import and Export 'SPSS', 'Stata' and 'SAS' Files. R package version 2.5.2. <a href="https://CRAN.R-project.org/package=haven">https://CRAN.R-project.org/package=haven</a>                                                                                                                                                                                                                                   |
| janitor    | 2.2.0   | Sam Firke (2023). janitor: Simple Tools for Examining and Cleaning Dirty Data. R package version 2.2.0. <a href="https://CRAN.R-project.org/package=janitor">https://CRAN.R-project.org/package=janitor</a>                                                                                                                                                                                                                                                              |
| MESS       | 0.5.9   | Claus Thorn Ekstrøm (2022). MESS: Miscellaneous Esoteric Statistical Scripts. R package version 0.5.9. <a href="https://CRAN.R-project.org/package=MESS">https://CRAN.R-project.org/package=MESS</a>                                                                                                                                                                                                                                                                     |
| psych      | 2.3.12  | William Revelle (2023). _psych: Procedures for Psychological, Psychometric, and Personality Research_. Northwestern University, Evanston, Illinois. R package version 2.3.12, <URL: <a href="https://CRAN.R-project.org/package=psych">https://CRAN.R-project.org/package=psych</a> >.                                                                                                                                                                                   |
| rcompanion | 2.4.34  | Mangiafico, Salvatore S. (2023). rcompanion: Functions to Support Extension Education Program Evaluation. version 2.4.34. Rutgers Cooperative Extension. New Brunswick, New Jersey. <a href="https://CRAN.R-project.org/package=rcompanion">https://CRAN.R-project.org/package=rcompanion</a>                                                                                                                                                                            |
| rstatix    | 0.7.2   | Alboukadel Kassambara (2023). rstatix: Pipe-Friendly Framework for Basic Statistical Tests. R package version 0.7.2. <a href="https://CRAN.R-project.org/package=rstatix">https://CRAN.R-project.org/package=rstatix</a>                                                                                                                                                                                                                                                 |
| tidyverse  | 2.0.0   | Wickham H, Averick M, Bryan J, Chang W, McGowan LD, François R, Golemund G, Hayes A, Henry L, Hester J, Kuhn M, Pedersen TL, Miller E, Bache SM, Müller K, Ooms J, Robinson D, Seidel DP, Spinu V, Takahashi K, Vaughan D, Wilke C, Woo K, Yutani H (2019). "Welcome to the tidyverse." <i>_Journal of Open Source Software_</i> , 4*(43), 1686. doi: 10.21105/joss.01686 (URL: <a href="https://doi.org/10.21105/joss.01686">https://doi.org/10.21105/joss.01686</a> ). |

## **1.9 Concurrent external control**

A remote prospective real world data study (full publication of data ongoing), running in parallel to the reported trial over 12 weeks (Jan-Apr/2023), was used as concurrent external control (6). Participants were recruited by an online survey querying inclusion criteria comparable to the reported trial (in brief: a history of AD (previously diagnosed by an HCP) and self-reported symptoms (dryness and/or redness and/or itching); not necessarily acute lesions, but at least 2 flare-ups in the last winter season; no systemic therapy with corticosteroids or calcineurin inhibitors). Within the external control study, participants applied their individually established skin care regimes and provided data regarding their skin condition and disease burden in a monthly online survey. The study population comprised a total of 304 participants, including 159 adults (mean age  $\pm$ SD:  $34.6 \pm 11.4$  years) and 145 children ( $5.5 \pm 3.5$  years). Participants reported their peak pruritus intensity by NRS-11 and eczema control by RECAP at baseline (D1) and every four weeks (D29, D57, D85) and tracked occurring flare-ups and corticosteroid use in an additional twice weekly online diary. The improvements over 12 weeks (proportional change from D1 to D85) for RECAP sum scores (N= 304, mean RECAP sum score  $\pm$ SEM: D1=  $12.23 \pm 0.31$ , D85=  $9.80 \pm 0.33$ , proportional improvement: -19.87%) and peak pruritus NRS-11 score (N= 304, mean NRS-11 score  $\pm$ SEM: D1=  $5.38 \pm 0.14$ , D85=  $4.46 \pm 0.15$ , proportional improvement: -17.01%) were used to estimate the external control response for each parameter. The estimated proportional improvement of the external control was adjusted to the mean baseline values (D1) of the herein reported study for the RECAP sum score (calculated mean absolute improvement: -2.17) or the peak pruritus NRS-11 score (-0.91), respectively, and depicted as external control response in Figures 2a and 2b with dotted lines.

## ***2 General information regarding instrumental measurements***

All instrumental measurements were performed in an air-conditioned room at a temperature of  $22 \pm 2$  °C and at  $50 \pm 7.5\%$  relative humidity. Before measurements, the subjects acclimatized in the room for at least 30 minutes.

## **2.1 Investigation of the organization and contents of epidermal lipids**

At baseline (D1) and after 12 weeks of application of the test product combination (D85), samples of a sub-panel of the study population (16 adult subjects) were taken via cyanacrylate stripping (*Lipbarvis*<sup>®</sup>) and analyzed regarding morphological changes of the intercellular lipids (i.e., length of lipid lamellae and area with no or substantially reduced occurrence of lipid lamellae in intercellular space) and lipid contents (ceramides (EOS, NP and AP), cholesterol and free fatty acids) of the Stratum corneum.

For sample extraction via non-invasive sampling of skin probes by *Lipbarvis*<sup>®</sup> stripping (LBV), an adhesive glue was added to a special carrier ( $\varnothing$  13 mm) which was then placed on top of the pre-moistened skin under slight pressure in order to remove any remaining air bubbles. After hardening, the carrier plus the now adhering skin layer was pulled off the skin surface. This procedure was repeated once at the same location in order to map the epidermal barrier. Three sample sets (two carriers per set) were taken on neighboring spots as indicated in **Supplementary Figures, Fig. S1**: one sample set for analysis via transmission electron microscopy (LBV-TEM) and two sample sets for analysis via high-performance thin layer chromatography (HPTLC) (LBV-LIP). Analysis of the collected *Lipbarvis*<sup>®</sup> samples was performed by MSD (Microscopy Services Dähnhardt GmbH, Flintbek, Germany) in accordance with the methodology outlined by MSD previously (7,8).

Briefly, LBV-TEM samples were processed as perpendicular sections (approximately 70 nm) via ultra-microtome and analyzed via

TEM to visualize and map the intercellular lipid structures (7,8). TEM-pictures were digitally colored and analyzed via semiautomatic image processing in order to determine the lengths of lipid lamellae and the area with no or substantially reduced occurrence of lipid lamellae in the intercellular space. LBV-LIP samples were extracted from the carriers via a hexane/ethanol mixture and ultrasonication and subsequently analyzed via high-performance thin-layer chromatography (HPTLC) to determine the lipid contents (7,8).

## **2.2 Investigation of the corneocyte maturity**

For investigation of the corneocyte maturity, probes of a subpanel of 32 subjects (adults and children) with very dry skin on the leg were taken on the outside of one lower leg at baseline (D1) and after 12 weeks of application of the test product combination (D85). Samples were taken via non-invasive, solvent-free sampling of skin probes by *D-squames*<sup>®</sup>. In short, a *D-squame*<sup>®</sup> disc was gently smoothed over the indicated area (**Supplementary Figures, Fig. S1**) by applying a uniform pressure for 30 seconds using a stamp to ensure consistent adhesion to the skin. Subsequently, the disc was pulled off the skin with one fluent and decisive movement and introduced into an Eppendorf tube, carefully placed with the “with glue” side inside the tube. This procedure was repeated once at the same location and the second disc was introduced into another tube, accordingly. All tubes were stored at -20 °C in a freezer after the sampling until shipment under dry ice.

*D-squame*<sup>®</sup> analysis was performed by QIMA (QIMA BIOALTERNATIVES SAS, Labège, France) based on the method of Hirao (9), which was further adapted according to literature (10,11). Briefly, the samples were thawed and the corneocytes were extracted from the matrix with a lysis buffer (3-times). The maturity of extracted corneocytes was subsequently determined by double staining with Nile red and involucrin. Fully mature corneocytes stain with Nile red which detects hydrophobicity but do not stain with involucrin. In contrast, immature corneocytes stain with involucrin only. The Nile red/involucrin ratio can be evaluated via picture processing to determine the degree of corneocyte maturity. Based upon the red/green signal ratio, the corneocytes were classified as red (ratio >1,8), mostly red (ratio 1,8-1,4), 50/50 (ratio 1,4-0,7), mostly green (ratio <0,7) or green (ratio <0,56). The mean of all ratios per assessment time and subject were provided as raw data (12).

## **2.3 Measurement of transepidermal water loss (TEWL)**

The transepidermal water loss (TEWL) is a non-invasive method to map barrier function of the skin and was assessed at baseline (D1) and after 12 weeks of application of the test product combination (D85). The TEWL was measured (one measurement per assessment time) for a subpanel of 32 subjects with very dry skin on the outside of one lower leg as indicated in **Supplementary Figures, Fig. S1**. The measurements were performed with the closed chamber system AQUAFLUX AF200 (Biox Systems Ltd., London, UK). Briefly, the cylindric chamber is placed at a defined distance to the skin to measure the insensible water evaporation from the skin. The chamber is closed to protect the air within against any disturbances from potential ambient air movements. Based on the linear distribution of humidity parallel to the axis of the chamber, the water vapor flux can be calculated from the humidity gradient via Fick's first law of diffusion.

### 3 References

1. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol* 2019; 181: 761-769. <https://doi.org/10.1111/bjd.17744>
2. Simpson E, Bissonnette R, Eichenfield LF, Guttman-Yassky E, King B, Silverberg JI, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): The development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol* 2020; 83: 839-846. <https://doi.org/10.1016/j.jaad.2020.04.104>
3. Simpson EL, Bissonnette R, Paller AS, King B, Silverberg JI, Reich K, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™): a clinical outcome measure for the severity of atopic dermatitis. *Br J Dermatol* 2022; 187: 531-538. <https://doi.org/10.1111/bjd.21615>
4. Eichenfield L, Boguniewicz M, Simpson E, Blauvelt A, Gooderham M, Lain E, et al. ONCE-DAILY ROFLUMILAST CREAM 0.15% FOR ATOPIC DERMATITIS: POOLED Results: FROM INTEGUMENT-1/2 PHASE 3 TRIALS. *Ann Allergy Asthma Immunol* 2023; 131: S91. <https://www.sciencedirect.com/science/article/pii/S1081120623008840>
5. Simpson E, Eichenfield L, Del Rosso J, Gooderham M, Hong HC-h, Kircik L, et al. Roflumilast Cream 0.15% in Patients with Atopic Dermatitis: Individual Patient Response from the Pooled INTEGUMENT-1 and INTEGUMENT-2 Phase 3 Trials. *SKIN The Journal of Cutaneous Medicine* 2024; 8: s372-s372.
6. Jahanshahi M, Gregg K, Davis G, Ndu A, Miller V, Vockley J, et al. The Use of External Controls in FDA Regulatory Decision Making. *Therapeutic Innovation & Regulatory Science* 2021; 55: 1019-1035. <https://doi.org/10.1007/s43441-021-00302-y>
7. Daehnhardt-Pfeiffer S, Surber C, Wilhelm KP, Daehnhardt D, Springmann G, Boettcher M, et al. Noninvasive Stratum Corneum Sampling and Electron Microscopical Examination of Skin Barrier Integrity: Pilot Study with a Topical Glycerin Formulation for Atopic Dermatitis. *Skin Pharmacol Physiol* 2012; 25: 155-161. <https://doi.org/10.1159/000336789>
8. Dähnhardt D, Surber C, Dähnhardt-Pfeiffer S. Influence of Topical Formulations: Lipid Lamella Organization and Lipid Composition of Stratum Corneum as a Surrogate Marker for Barrier Integrity. *pH of the Skin: Issues and Challenges*: S.Karger AG, 2018: p. 166-172.
9. Hirao T, Denda M, Takahashi M. Identification of immature cornified envelopes in the barrier-impaired epidermis by characterization of their hydrophobicity and antigenicities of the components. *Exp Dermatol* 2001; 10: 35-44. <https://doi.org/10.1034/j.1600-0625.2001.100105.x>
10. Mohammed D, Matts PJ, Hadgraft J, Lane ME. Depth profiling of stratum corneum biophysical and molecular properties. *Br J Dermatol* 2011; 164: 957-965. <https://doi.org/10.1111/j.1365-2133.2011.10211.x>
11. Raj N, Voegeli R, Rawlings AV, Gibbons S, Munday MR, Summers B, et al. Variation in stratum corneum protein content as a function of anatomical site and ethnic group. *Int J Cosmet Sci* 2016; 38: 224-231. <https://doi.org/10.1111/ics.12274>
12. Jarrold B, Kaczvinsky J, Matts P, Osborne R, Weitz S. Use of a cosmetic moisturizer promotes corneocyte maturity. *J Am Acad Dermatol* 2010; 62: AB62. [http://www.sciencedirect.com/science/article/pii/S0190-9622\(09\)02153-7](http://www.sciencedirect.com/science/article/pii/S0190-9622(09)02153-7)