

Long-term Progressive Improvement of Atopic Dermatitis by an Herbal Emollient Plus Combination in a 12-week Clinical Trial

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Atopic dermatitis is a chronic inflammatory skin disease characterized by flare-ups of inflamed, dry, and itchy skin affecting over 200 million people worldwide. "Emollients plus" containing active cosmetic ingredients such as herbal extracts and phytochemicals have the potential to surpass the efficacy of conventional emollients, while avoiding side effects associated with pharmacological interventions. The reported 12-week clinical trial (NCT05790083) evaluated long-term efficacy and tolerability of oil-in-water emulsions BNO 3731 and BNO 3732 containing ginger extract and cannabidiol as basic emollient therapy for atopic dermatitis. A total of 100 adults and children with a history of atopic dermatitis were included and applied BNO 3732 (body lotion) twice daily and BNO 3731 (intensive care product) as needed. Over 12 weeks the emollients plus combination led to sustained improvement of peak pruritus and patient-reported outcome measures, i.e., "Recap of atopic eczema". Objective dermatological evaluation showed progressive improvements for vIGA-ADTM and isolated symptoms, i.e., erythema and dryness. Instrumental analysis of intercellular lipid contents and lipid lamellae organization in the stratum corneum demonstrated recovery of the epidermal barrier integrity. The clinical results provide evidence on the efficacy of herbal emollients plus beyond mere moisturizing and occlusive properties. BNO 3731 and BNO 3732 were very well tolerated.

Key words: atopic dermatitis; basic emollient therapy; clinical trial; emollient plus; herbal ingredients; phytochemicals.

Submitted Jan 24, 2025. Accepted after revision May 20, 2025

Published Jun 18, 2025. DOI: 10.2340/actadv.v105.43026

Acta Derm Venereol 2025; 105: adv43026.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by flares of inflamed, dry, and itchy skin. The worldwide prevalence is increasing, with over 200 million people affected (1). As no cure for AD is available, the treatment goal is symptomatic management using pharmacological and non-pharmacological interventions (2). Patients suffering from AD often have a reduced quality of life, with one of the most burdensome symptoms being itch (3). Therefore, the control of itch

SIGNIFICANCE

Basic emollient treatment is a cornerstone in the long-term management of atopic dermatitis. In recent years, emollients plus with active cosmetic ingredients have emerged as effective treatment options beyond simple moisturizers and occlusives. To evaluate the efficacy of novel (cosmetic) emollients, high-quality clinical trials are essential. Therefore, a new combination of emollients (oil-in-water emulsions) containing ginger extract and cannabidiol was tested over 12 weeks in patients with atopic dermatitis. The products provided sustained itch relief, progressive improvement of visible symptoms, and substantial recovery of the skin barrier. Herbal emollients plus are able to improve basic emollient therapy beyond conventional emollients.

should be the central focus of treatment and a primary therapeutic goal (4).

A key feature of the pathophysiology underlying the appearance and eczematous lesions of AD skin is a compromised skin barrier integrity, which contributes to the development of itch and is manifested by distinct physiological changes (4, 5). For instance, the amounts of certain epidermal lipids (e.g., ceramides EOS, NP and AP, cholesterol, and free fatty acids) are reduced (6). Besides, a disrupted lipid organization represented by a shortened length of lipid lamellae and enlarged areas with no or significantly reduced occurrence of lipid lamellae in the intercellular space of the stratum corneum (SC) can be observed (7–10). A reduced ratio of mature to immature corneocytes in the SC of AD patients due to a disturbed differentiation has been reported as well (7, 11).

Basic therapy with emollients remains the cornerstone of AD treatment (12, 13), as recommended by the European guideline as well as by the 2022 consensus report by the European Federation of Allergy and Airways Diseases Patients' Associations (EFA) (13, 14). Despite their significance, the therapeutic efficacy of conventional emollients is limited. Primarily containing moisturizing and/or occlusive agents, they effectively increase epidermal hydration and reduce transepidermal water loss; however, do not specifically target the mechanisms underlying skin irritation and barrier dysfunction, which in turn are associated with itch perception (4).

A recent strategy to improve basic emollient therapy is the formulation of emollients with active, non-medicated

substances (active cosmetic ingredients, ACIs), resulting in so-called "emollients plus", which have been recognized by the European Guideline on Atopic Eczema (12, 13). These next-generation topicals aim to complement the mere occlusive and moisturizing properties of conventional emollients by specifically addressing bothersome symptoms such as erythema or itch and thereby reduce the need for pharmacological interventions with topical corticosteroids (TCS) or calcineurin inhibitors (TCI).

Herbal ingredients have a great potential as ACIs and, accordingly, herbal emollients plus have been suggested to exceed the effects of mere emollients (10, 15, 16). A previous publication reported synergistic anti-inflammatory and anti-oxidative properties of a ginger extract and cannabidiol (CBD) *in vitro* and proposed a putative mode of action of these ACIs. For instance, ginger extract and CBD reduced TNF- α -induced NF- κ B activation in an epidermal cell line (HaCaT) as well as the release of inflammatory cytokines including TNF- α , IL-6, and IL-8 from primary keratinocytes (NHEK), and decreased LPS-induced NO release in macrophages (17). The oil-in-water emulsion BNO 3731, containing a combination of ginger extract and CBD, showed fast and significant improvement of visible AD symptoms such as erythema, dryness, scaling, and papules as well as rapid reduction of peak pruritus along with very good tolerability in a 5-day clinical trial including an emollient plus comparator product (17).

The prospective interventional clinical trial reported here assessed the efficacy and tolerability of an emollient plus combination comprising both the intensive care product BNO 3731 and corresponding body lotion BNO 3732 in adults and children suffering from AD over 12 weeks. In addition to objective dermatological assessments, evaluation of itch intensity, and patient-reported outcome measures (PROMs), a focus was set on the investigation of the barrier integrity in a subgroup of

adults, by assessing epidermal lipid content, lipid lamellae organization, and corneocyte maturity.

MATERIALS AND METHODS

Investigational cosmetic products

Bionorica® Derma Line "Lotion" (BNO 3732) (body lotion) and "Atopi Intensivpflege" (BNO 3731) (intensive care) are non-occlusive oil-in-water emulsions containing the ACIs ginger (lipophilic CO₂ extract) and CBD (synthetic) (for details see Appendix S1). The products were blinded with black tape and the subjects were not informed about the quality of the products.

Clinical trial design

Long-term efficacy of the product combination was assessed via a prospective, interventional, monocentric trial. To assure complete epidermal turnover and demonstrate progressive long-term effects, a trial duration of 12 weeks was purposely selected, as the approximate physiological turnover of the SC is around 28 days (Fig. 1) (18). A remote real-world data (RWD) study was implemented as a concurrent external control for selected patient-reported outcomes as well as for the occurrence of flare-ups and related corticosteroid use (19). The prospective study collected and analysed RWD on disease burden and emollient use in 304 adults and children with AD, aiming to assess the real-world effectiveness of basic emollient therapy in AD and was carried out in parallel (01/2023-04/2023) with the reported trial (for details see Appendix S1).

Participant selection

A population of $n=100$ patients with atopic dermatitis was enrolled with $n=94$ patients analysed (5 subjects dropped out without and 1 subject dropped out with

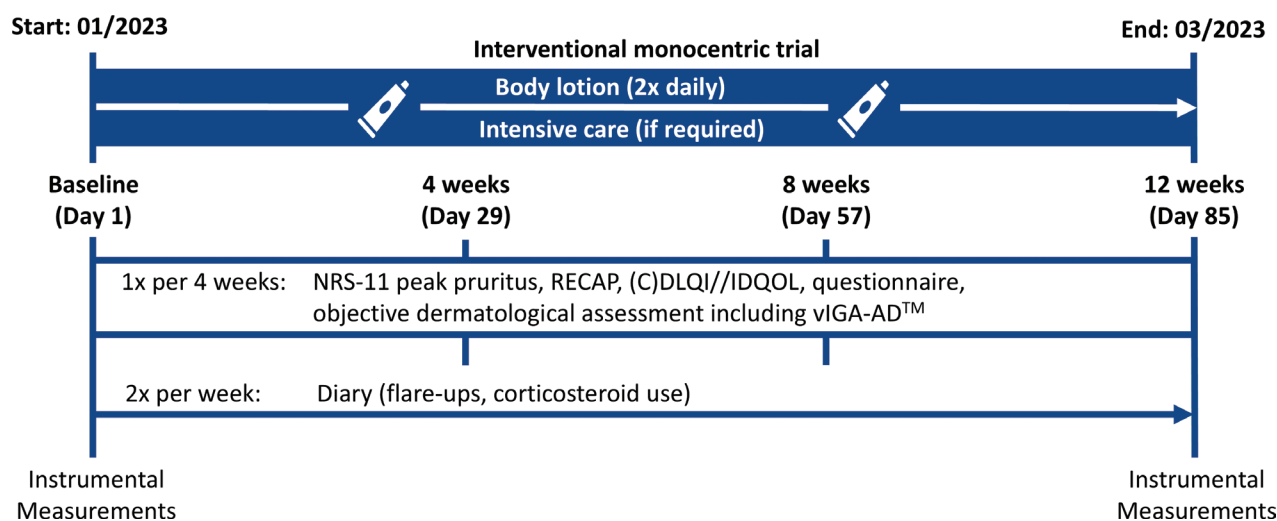


Fig. 1. Trial design of the 12-week monocentric trial.

relation to test product(s)). The patients (21 male [22%], 73 female [78%]) had a history of AD with at least 2 flare-ups in the previous winter season but did not necessarily present with acute lesions at inclusion. Patients with current systemic AD therapies or regular, proactive use of TCS/TCI were excluded; therefore the population can be defined as having "mild atopic dermatitis" in accordance with the stepped-care plan of the European Guideline on Atopic Eczema (13). The population included children/adolescents (≥ 2 –17 years, mean age $\pm$ SD: 8.9 ± 3.8 years) and adults (≥ 18 years, mean age $\pm$ SD: 43.6 ± 15.3 years) in a ratio of roughly 1:1 with a mean age of 27.7 ± 20.8 years (mean $\pm$ SD). Complete inclusion and exclusion criteria are provided in Appendix S1.

Treatment schedule

Patients were advised to use the body lotion twice daily (morning and evening) as needed on the whole body including the face, but at least on arms, legs, abdomen, and lower back, according to normal use conditions. Patients were instructed to use the intensive care product as required on affected body areas in addition to the body lotion.

Clinical assessment

Subjective clinical assessment followed the recommendations by the Harmonising Outcome Measures for Eczema (HOME) initiative including the validated PROMs "Recap of atopic eczema" (RECAP) (20) and (Children's) Dermatology Quality of Life Index (CDLQI, age 4–15 years/DLQI, age ≥ 16 years)/Infants' Dermatitis Quality of Life Index (IDQOL, age < 4 years) (21–23). Itch was evaluated by the PRO tool peak pruritus numerical rating scale (NRS-11) (24, 25). The occurrence of flare-ups and flare-up-related TCS use was documented in twice-weekly online diary reports. Visible skin alterations were assessed by experienced dermatologists as individual objective symptoms on a proprietary scale and globally via the validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-ADTM) (26). To evaluate the epidermal barrier integrity, lipid composition and organization within the interstitial space in the SC were analysed via non-invasive Lipbarvis[®] sampling (7, 8) (Fig. S1). The samples were subsequently evaluated via transmission electron microscopy (TEM) based methods for mapping and visualization of the lipid lamellae. The contents of intercellular lipids (ceramides (EOS, NP, and AP), cholesterol and free fatty acids) were measured via high-performance thin-layer chromatography (HPTLC). Corneocyte maturity was determined via D-Squame[®] analysis with subsequent double staining (Nile red/involucrin) and evaluation of the emerging red/green signal ratio (27). Transepidermal water loss (TEWL) was measured with a closed chamber system AQUAFLUX AF200 (Biox Systems Ltd, London, UK). For details see Appendix S1.

Statistical analysis

Descriptive statistics were calculated for raw data and calculated values. A significance level of 0.05 (alpha) was chosen for statistical analysis. No adjustments for multiplicity were made. Details are provided in Appendix S1. The computation of the statistical data was carried out with SAS for Windows (SAS Institute GmbH, Heidelberg, Germany) and R V4.1.3 (see Appendix S1; R Foundation for Statistical Computing, Vienna, Austria) (28).

Ethics approval for clinical trials

The trial (NCT05790083) was reviewed by an independent institutional review board (IRB) of the executing clinical research organization (SGS proderm GmbH, Schenefeld, Germany) for ethical approval.

RESULTS

Subjective assessment and diary

The subjective AD burden was assessed using RECAP, peak pruritus NRS-11, and (C)DLQI/IDQOL. Baseline mean RECAP sum scores confirmed that the included population was representative of a patient collective suffering from AD (adults ≥ 18 years: 10.9; SD 5.4; SEM 0.8; $n=51$; children/adolescents < 18 years: 10.9; SD 5.1; SEM 0.8; $n=43$), being in line with literature (29) (adults ≥ 18 years: 14.0; SD 6.6; $n=218$; children/adolescents < 18 years: 13.3; SD 7.4; $n=162$), and proprietary data (adults ≥ 18 years: 13.0; SD 5.5; SEM 0.4; $n=159$; children < 18 years: 11.4; SD 5.1; SEM 0.4; $n=145$; data from concurrent external control study, see Appendix S1).

Over the 12-week trial, a significant improvement ($p<0.001$) in mean RECAP sum score with a fast onset in reduction of 54% in the first 4 weeks was seen (Fig. 2A). Similarly, peak pruritus was significantly ($p<0.001$) reduced by 53% after 4 weeks, with 64% of participants classifying as positive responders having reached the minimal clinically important difference (MCID) of 2 points on the NRS-11 scale (Fig. 2B/C) (24). The significant reductions for RECAP sum score and peak pruritus NRS-11 score were sustained over 12 weeks and clearly exceeded the external control response (Fig. 2A/B, dotted line; for more details see Appendix S1) (19).

The skin-related quality of life for adults (≥ 16 years) and children (4–15 years) significantly increased in the first 4 weeks according to the DLQI and CDLQI, respectively, followed by a slight, yet progressive improvement over the remaining 8 weeks (Fig. 2D/E). The data for infants (< 4 years, IDQOL) were not analysed due to the small number of participants ($n=3$).

Only 35% of subjects ($n=33$) documented at least 1 flare-up in the online diary within the 12 weeks and in only 12% of these cases did the participant use a TCS

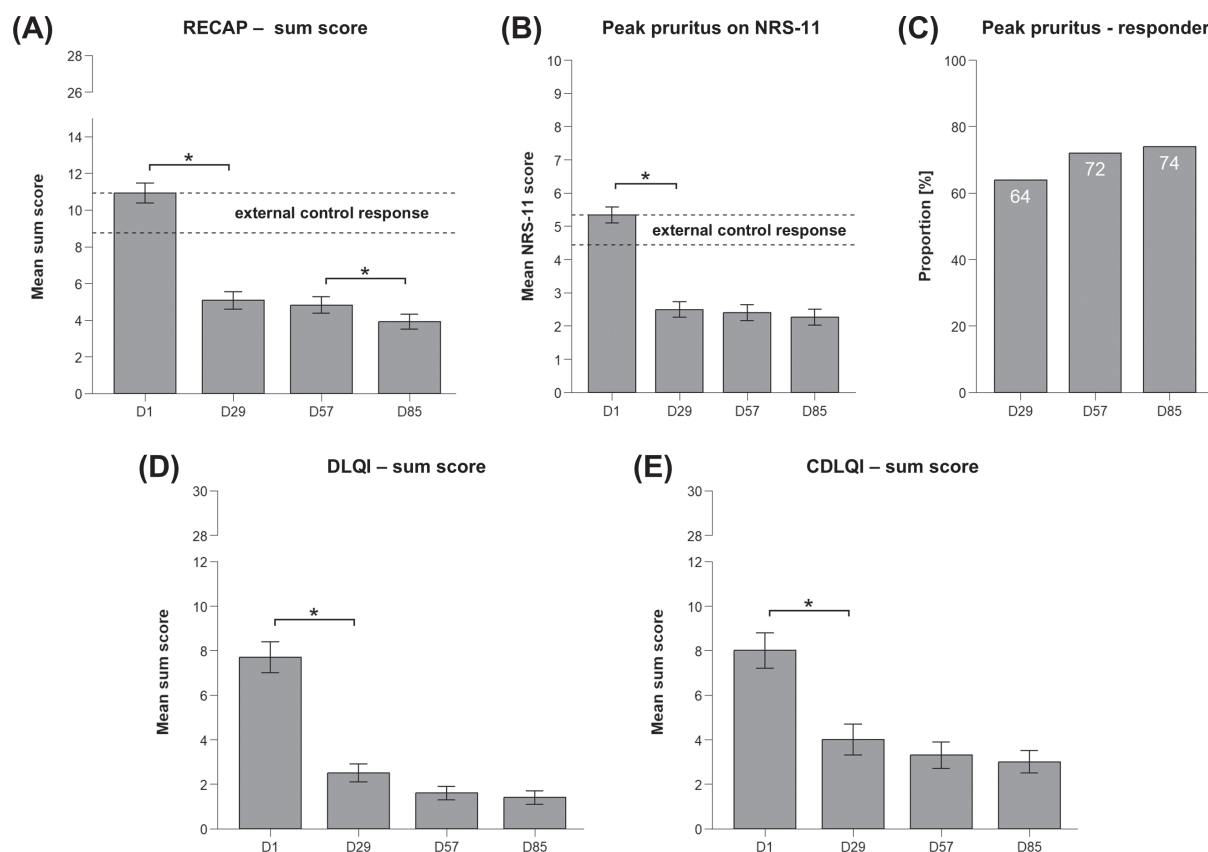


Fig. 2. Subjective evaluation and quality of life. (A) RECAP sum score, $n=92-94$, two-sided paired t -test, data represent mean $\pm$ SEM, $*p \leq 0.05$, Banning (30): 0–1: completely controlled, 2–5: mostly controlled, 6–11: moderately controlled, 12–19: a little controlled, 20–28: not at all controlled, dotted line: external control response (see Appendix S1). (B) Subjective evaluation of peak pruritus according to NRS-11 scale, $n=92-94$, two-sided paired Wilcoxon signed-rank test, data represent mean $\pm$ SEM, $*p \leq 0.05$, dotted line: external control response (see Appendix S1). (C) Proportion of positive responders (%) according to an improvement of peak pruritus by ≥ 2 points defined as responder achieving MCID (24). (D) DLQI sum score, $n=45-48$ (age ≥ 16 years), two-sided paired t -test, data represent mean $\pm$ SEM, $*p \leq 0.05$, Banning (31): 0–1: no effect at all on patient's life, 2–5: small effect, 6–10: moderate effect, 11–20: very large effect, 21–30: extremely large effect on patient's life. (E) CDLQI sum score, $n=38-39$, two-sided paired t -test, data represents mean $\pm$ SEM, $*p \leq 0.05$, Banning (32): 0–1: no effect on child's life, 2–6: small effect, 7–12: moderate effect, 13–18: very large effect, 19–30: extremely large effect on child's life.

in relation to the flare-up. Overall, 93% of participants did not use any TCS during the trial. Conversely, in the analogous online diary of the 12-week concurrent RWD control, 96% of participants reported at least 1 flare-up and 73% of participants reporting a flare-up subsequently used a TCS at least once (19).

At the end of the reported trial (D85), more than 90% of the participants were (very) satisfied with the product combination BNO 3731 and BNO 3732 and over 96% of participants stated that the test products were well tolerated.

Objective assessment

In order to substantiate the subjective results, objective AD symptoms were assessed by trained dermatologists at the study centre at the beginning and every 4 weeks thereafter. Significant improvements in erythema, dryness, scaling, and papules were observed at the first assessment (D29) and were sustained and/or, in most cases, even progressive over the following 8 weeks of product application (Fig. 3A/B). Correspondingly, mean vIGA-AD™ scores significantly decreased by 63%

over 12 weeks (Fig. 3C). At the end of the trial, 88% of participants were classified as vIGA-AD™ responders (MCID: reduction ≥ 1 point) (26) and 59% had achieved vIGA-AD™ success (improving from score 4/3/2 at baseline by ≥ 2 points to score 1/0) (26) reflecting (almost) complete skin clearance (Fig. 3D).

Instrumental measurements

Stratum corneum sampling by cyanoacrylate stripping (Lipbarvis®) in an adult subpanel ($n=16$) and subsequent HPTLC analysis found increased contents of all measured intercellular SC-lipids after 12 weeks of test product application, reaching the level of significance ($p \leq 0.05$) for ceramide EOS, ceramide NP, free fatty acids, and cholesterol (Fig. 4).

Accordingly, TEM analysis of Lipbarvis® samples indicated a significant ($p < 0.001$) increase in the mean length of lipid lamellae (D1: mean $\pm$ SEM: 61.08 ± 2.17 nm/1,000 nm² to D85: 196.23 ± 4.01 nm/1,000 nm²; $n=16$) (Fig. 5C), reaching a value comparable to healthy skin (approx. 200 nm/1,000 nm²) after 12 weeks (8).

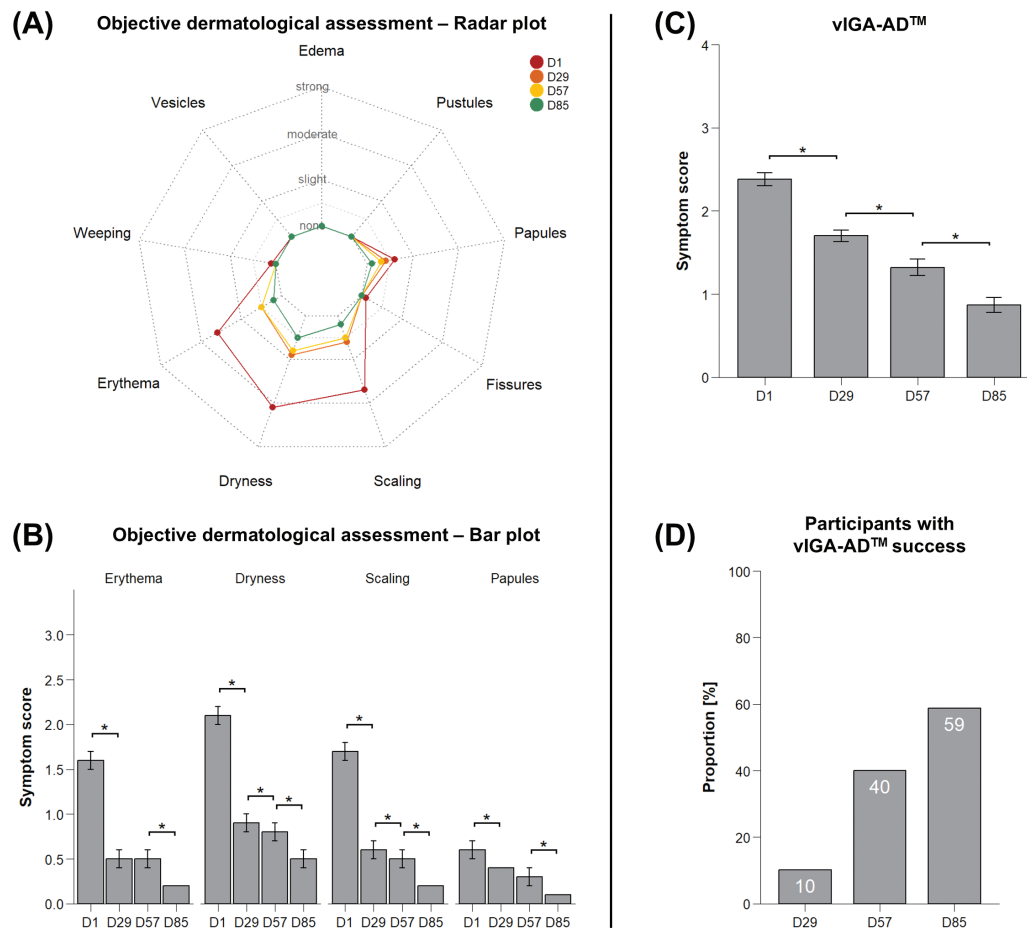


Fig. 3. Objective dermatological evaluation. (A) Radar plot of all parameters of objective dermatological assessment. (B) Symptom score for erythema, dryness, scaling, and papules objectively assessed by a dermatologist, $n = 92-94$, two-sided paired Wilcoxon signed-rank test, data represent mean $\pm$ SEM, $*p \leq 0.05$; scoring: 0 = none, 0.5 = very slight, 1 = slight, 2 = moderate, 3 = strong. (C) vIGA-AD™ score, $n = 92-94$, test: Wilcoxon signed-rank test, data represent mean $\pm$ SEM, $*p \leq 0.05$, scoring (26): 0: clear, 1: almost clear, 2: mild, 3: moderate, 4: severe. (D) Proportion of subjects achieving vIGA-AD™ success (improvement from score ≥ 2 at baseline ($n = 79-80$) by ≥ 2 points to vIGA-AD™ score of ≤ 1 at later assessment time) (26) in %.

Finally, a novel analysis method quantified areas with no or substantially reduced lipid lamellae versus areas with regular lipid lamellae structure (Fig. 5A). The mean area of impaired lipid lamellar structure, indicative of epidermal barrier defects, was significantly ($p < 0.001$) decreased by 94% (from 53% to 3%) at D85 (Fig. 5B). Taken together, the Lipbarvis® sampling-based evaluations evidenced complete recovery of the intercellular lipid organization in the evaluated subpanel of adults.

In a larger subpanel of adult and child participants ($n = 32$), D-Squame® analysis was carried out to assess the corneocyte maturity in the epidermis. The ratio of mature to immature corneocytes was significantly ($p < 0.001$) increased after 12 weeks of test product application (D1: mean $\pm$ SEM: 1.260 ± 0.025 to D85: 1.378 ± 0.019 ; $n = 32$; Fig. 5D), indicating that the test products supported physiological corneocyte differentiation (11).

Despite the clear improvements seen for all measurements assessing epidermal barrier integrity in a direct manner, the TEWL was not significantly reduced for the evaluated subpanel ($n = 32$) at the end of the trial period (mean values $\pm$ SEM; D1: 13.9 ± 0.7 g/

m^2h ; D85: 13.3 ± 0.8 g/ m^2h ; $p = 0.325$). Of note, TEWL values for healthy subjects on the lower leg (shin and calf) have been estimated to be in the range of around 2.8–10.2 g/ m^2h (33, 34) and reported to be increased up to 30 times for compromised epidermis (35).

DISCUSSION

The reported trial assessed the long-term efficacy and tolerability of oil-in-water emulsions BNO 3732 and BNO 3731 containing the ACIs ginger extract and CBD in adults and children suffering from AD. Combining vehicle-type substances with ACIs (13), emollients plus have the potential to exceed the effects of ordinary emollients and skin care routines in basic emollient therapy for AD, which has been indicated in previous clinical studies (10, 16, 36, 37).

Regular application of the test products over 12 weeks significantly improved eczema control, skin-related quality of life, and itch perception as evaluated by PROMs and peak pruritus NRS-11 beyond an external control response derived from complementary RWD of conventional skin

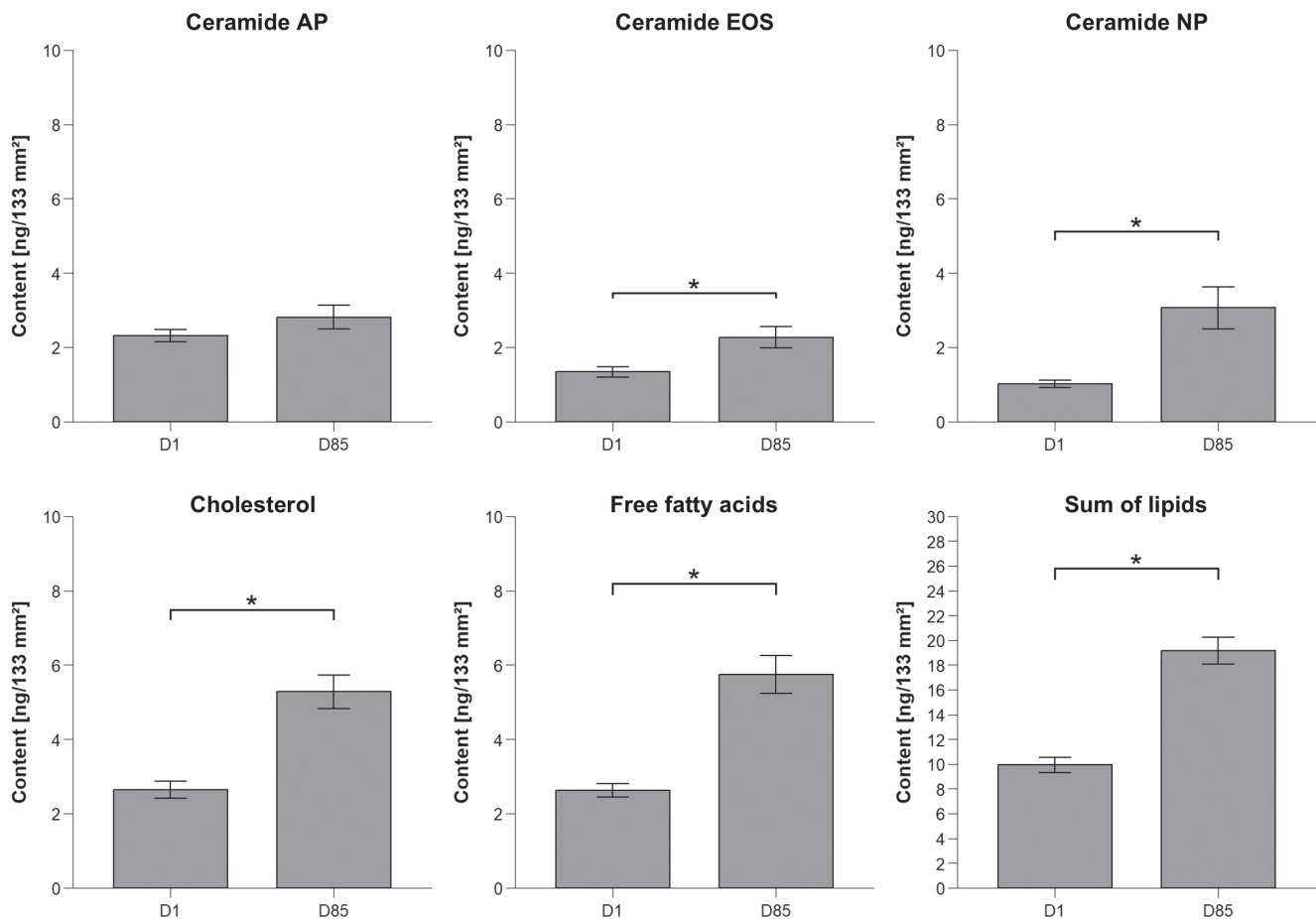


Fig. 4. Lipid analysis. Contents of intercellular lipids at baseline (D1) and after 12 weeks (D85) of test product(s) application in [ng/133 mm²]; $n = 16$, test: two-sided paired t -test, data represent mean $\pm$ SEM, * $p \leq 0.05$.

care regimes (19). In particular, itch, reportedly the most prevalent, severe, and burdensome symptom of AD, was strongly reduced within the first 4 weeks and remained at a low level throughout the application period with BNO 3731 and BNO 3732 (3). These results complement the previously reported rapid effects in short-term application of the intensive care product BNO 3731 alone, where significant improvements were already observed after 24 h (17). As alleviating itch is the primary therapeutic goal of AD patients, emollients plus providing both fast and long-lasting relief of pruritus are particularly valuable in long-term AD control, e.g., to reduce the need for pharmacological intervention (3). This is substantiated by the diary reports, as merely 12% of participants documented applying TCS in direct relation to a flare-up during the 12-week application of the emollient plus combination BNO 3731 and BNO 3732. In the concurrent RWD study evaluating individually established skin care regimes, 96% of participants reported at least 1 flare-up during the 12-week period and 73% of these applied a TCS related to a documented flare-up (19).

The sustained subjective improvements were complemented by progressive amelioration of objective AD manifestations including erythema, dryness, scaling,

and papules. In respect of the global assessment, 59% of participants with a vIGA-ADTM score of ≥ 2 at baseline achieved complete or almost complete skin clearance by means of the vIGA-ADTM treatment success.

Furthermore, instrumental SC analysis in a subpanel of adults revealed a significant increase of epidermal lipids along with reconstitution of the lipid lamellar structural organization (8, 38). Notably, these lipids were not utilized as individual excipients for BNO 3732 or BNO 3731. Thus, the increased contents indicate *de novo* lipid synthesis (9, 39). Such changes in the SC lipid composition have already been reported after 5-week application of a marketed body lotion and attributed to the probable ability of human skin to produce elongated fatty acids when provided with suitable precursors (39). Moreover, the physiological lipid synthesis and corneocyte differentiation are very likely supported by anti-inflammatory activity associated with a modulation of the endocannabinoid system, as discussed earlier for the ACI combination ginger extract and cannabidiol (17).

In the present trial, a novel approach towards the assessment of barrier integrity by direct quantification of areas with no or substantially reduced lipid lamellae illustrated the recovery of structural defects in lipid orga-

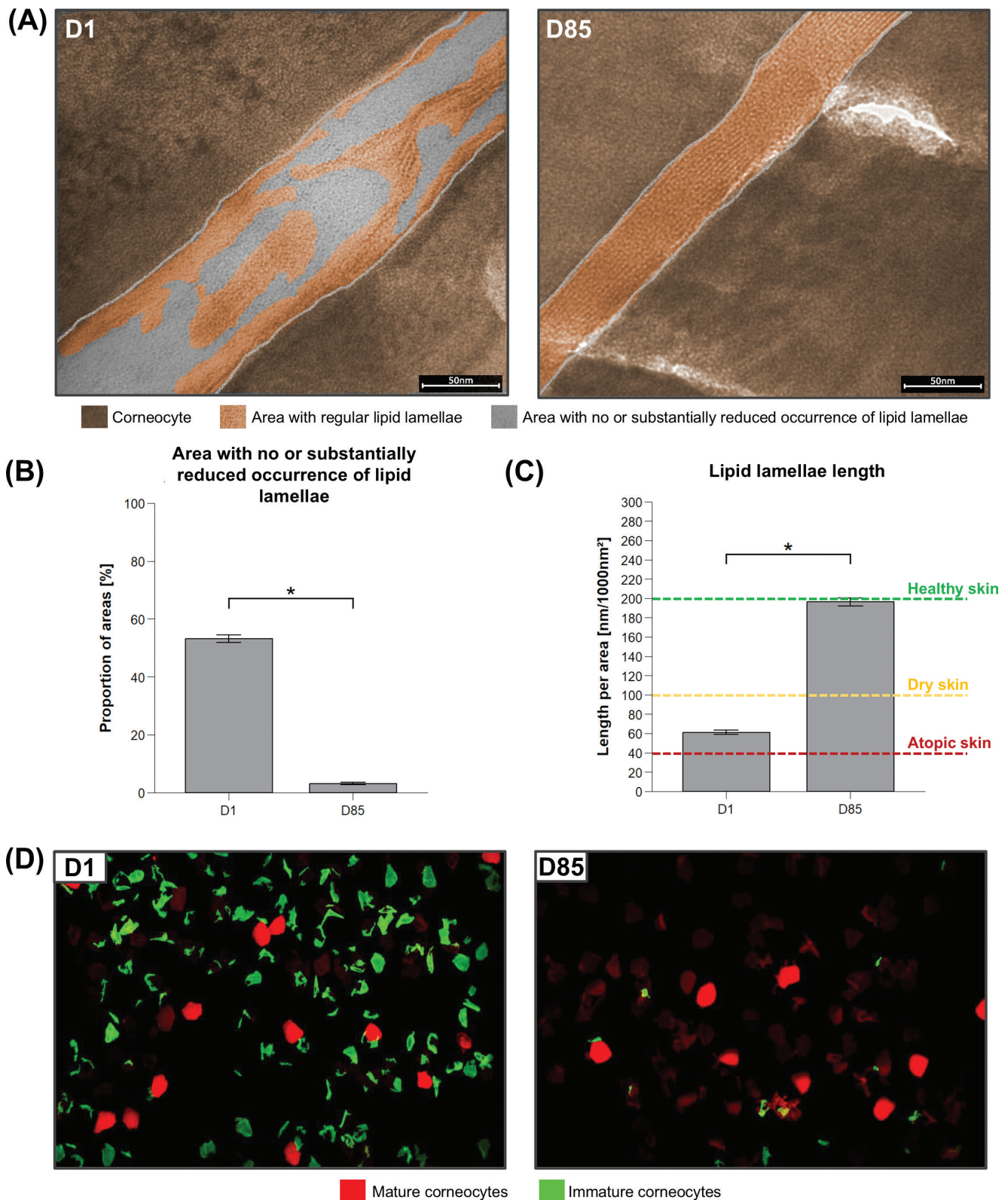


Fig. 5. Analysis of lipid lamellae and corneocyte maturity. (A) Colored TEM picture of Lipbarvis® samples taken at baseline (D1) and after 12 weeks (D85), dark brown: corneocyte, orange/brown: areas with regular lipid lamellae, grey: areas with no or substantially reduced lipid lamellae. (B) Proportion of areas with no or substantially reduced lipid lamellae at baseline (D1) and after 12 weeks of test product(s) application (D85) as percentage of total intercellular area, $n = 16$, two-sided paired t -test, data represent mean $\pm$ SEM, $*p \leq 0.05$. (C) Length of intercellular lipid lamellae (nm/1,000 nm²) at baseline (D1) and after 12 weeks of test product(s) application (D85), $n = 16$, two-sided paired t -test, data represent mean $\pm$ SEM, $*p \leq 0.05$, indication of skin condition according to Dähnhardt et al. (8). (D) Microscope image of exemplary D-Squame® corneocyte samples (of 1 subject) post-staining at baseline (D1) and after 12 weeks of test product(s) application (D85), red: mature corneocytes, green: immature corneocytes.

nization of compromised AD skin, as shown in Fig. 5. Notably, the enhanced epidermal barrier integrity was not associated with a significant TEWL decrease. However, as baseline TEWL values were in the range of the skin of healthy subjects, it is plausible that the implemented methodology was not sensible for the included population. Additionally, TEWL represents an indirect barrier measure that does not necessarily reflect barrier integrity compared with electron microscopic visualization (7).

Poor patient adherence is a major hindrance to AD control and has been reported to be insufficient in the real-world setting, particularly for basic emollient therapy (40). Based on the long-lasting efficacy, the high tolerability (only 1 subject with treatment-related adverse events), and the patient-reported product satisfaction, high adherence under real-world conditions can be expected for BNO 3732 and BNO 3731, especially in light of the general acceptance of sustainable plant-based formulations (41).

Limitations

Limitations of the reported trial include the absence of a dedicated control group, which was addressed by the implementation of an external RWD control. Furthermore, the subpanel for instrumental skin barrier analysis was reduced compared with the complete study population ($n=32/16$); nevertheless the observed results were significant. Lastly, there were no instructions regarding the amount of products to be used, so a correlation between the magnitude of the effects and the used amounts of the product combination cannot be drawn.

CONCLUSION

Oil-in-water emulsions BNO 3732 and BNO 3731 containing the ACIs ginger extract and cannabidiol with anti-inflammatory and antioxidative *in vitro* activities are efficacious beyond mere moisturizing and occlusive properties by providing sustained relief of itch, long-lasting improvement of objective AD symptoms, and stabilization of the epidermal permeability barrier. The results show clearly that herbal emollients plus specifically addressing epidermal irritation and pruritus are able to improve basic emollient therapy and offer additional benefits to AD patients beyond conventional emollients. Considering the rising therapeutic significance of emollients plus in AD, clinical studies comparing different products will be of increasing interest for identifying superior formulations in future.

ACKNOWLEDGEMENTS

Medical writing support was provided by Dr. Michael Wördehoff (co.medical, Berlin, Germany).

Funding sources: This trial was funded by Bionorica SE (Neumarkt in der Oberpfalz, Germany).

IRB approval status: The trial was reviewed by an independent institutional review board for ethical approval (SGS proderm GmbH, Schenefeld, Germany).

Conflict of interest disclosures: LH, SA, RZ, CN, KM, NM, HS, and CA are/were employed by Bionorica SE (Neumarkt in der Oberpfalz, Germany). CA is named as inventor on a patent application for compositions containing cannabidiol and an extract from ginger (WO 2023/046730). All authors received medical writing support from co.medical (Berlin, Germany).

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