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Stand-alone Emollient Treatment Reduces Flares After Discontinuation of Topical Steroid Treatment in Atopic Dermatitis: A Double-blind, Randomized, Vehicle-controlled, Left-right Comparison Study

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Prevention of the flares is a main goal in the long-term treatment of atopic dermatitis (AD). Therefore we investigated the efficacy of a water-in-oil emollient, containing licochalcone A, omega-6-fatty acids, ceramide 3 and glycerol, for prevention of the flares in adults with mild to moderately severe AD, treated with topical steroids, that led to clearing of the inflammatory lesions and had been discontinued prior to inclusion. The study was a 12-week, double-blind, randomized, vehicle-controlled, left-right comparison test with the number of relapses, defined as re-occurrence of erythema for at least 3 consecutive days, considered the primary outcome. Compared with the vehicle, the active formulation significantly reduced the number of relapses and maintained the barrier homeostasis of the respective arm. To the best of knowledge, this is the first study to show prevention of the AD flares by the use of stand-alone emollient treatment, based on comparison with the corresponding vehicle while excluding concomitant/rescue medications.

Key words: atopic dermatitis; maintenance treatment; emollients; skin barrier; licochalcone A; omega-6 fatty acids.

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Atopic dermatitis (AD), or eczema, is a chronic, relapsing and intensely pruritic inflammatory skin disease resulting from a complex interplay of host-related and environmental factors (1–4). The recurrent eczematous lesions with age-specific morphology and distribution usually occur for the first time in infancy or early childhood and may persist throughout life in up to 60% of the cases of moderate or severe childhood eczema (5). The management of AD relies on efficient control of the flares by treatment of the acute inflammatory symptoms in parallel with identification and avoidance of the relevant triggering factors and maintenance of the skin barrier homeostasis (6–9). With the recognition of the critical role of the epidermal barrier to disease pathogenesis and associated allergic comorbidities (3, 10–12), recent studies have investigated whether emollient treatment that aims at restoration of the barrier function might be a safe and efficient strategy for disease prevention and reducing the risk of flares (13, 14). Although several investigations provide initial evidence for reduced risk and prolonged time to flare (15–20), the interpretation of the published results has been limited by lack of comparison with the respective vehicle controls or the concomitant use of topical prescription medication, notably steroids and calcineurin inhibitors. As emollients are fundamental to the long-term disease management, the present double-blind, randomized, left–right comparison study investigated the effects of a water in oil (w/o) formulation on the rate of relapses, compared with the corresponding vehicle, while excluding possible confounders, such as concomitant use of anti-inflammatory or rescue medication.

MATERIALS AND METHODS

Study design and population

The study was a double-blind, prospective, randomized, vehicle-controlled left-right comparison test of maximum 12 weeks duration. Eligible for participation were female and male volunteers aged 18–65 years with AD according to the UK Working Party Criteria (21) and mild to moderately severe inflammatory lesions, located symmetrically on both forearms/arms within the last 4 weeks prior to inclusion, that had been treated with topical steroids (class I–III) and resolved completely, so that the topical steroids had been discontinued before entering the study (**Fig. 1**). The exclusion criteria were defined as follows: (*i*) manifest oedema, papules, exudation or crusts in the test area; (*ii*) erythema > 1 or/and excoriations > 2, based on SCORing Atopic Dermatitis (SCORAD) intensity parameters (local SCORAD); (*iii*) local SCORAD in the test area >5. Further exclusion criteria included clinical manifestations of another skin disease in the test area, treatment with immunosuppressive or antimicrobial agents and/or ultraviolet (UV) light treatment in the last 2 weeks prior to

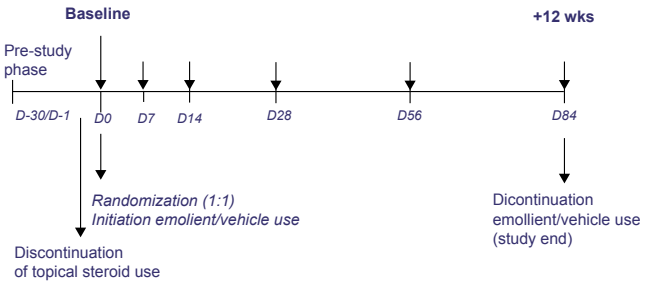

Fig. 1. Study outline.

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screening, known or suspected contact sensitization to the test formulation ingredients, concomitant severe systemic disease and questionable compliance.

Twenty-six volunteers aged 19–64 years (21 women and 5 men; median age 24.5 years) who met all the inclusion and none of the exclusion criteria were enrolled in the study between March 2014 and March 2015 (no inclusion between May and October 2014). Upon entering the study (baseline) the left and right forearms/arms of each volunteer were randomized to receive either the test w/o formulation or the vehicle, to be applied twice daily on the entire forearms and arms, for a maximum of 12 weeks or until a clinical relapse, defined as the presence of erythema on at least one arm for 3 consecutive days, whatever earlier, occurred. The test formulation contained glycerol (10%), evening primrose (6%) and grape-seed (6%) oil, rich in omega-6-fatty acids, ceramide 3 and licochalcone A (<1%) as active components that aimed to increase the stratum corneum (SC) hydration, enhance the barrier function and reduce inflammation. The vehicle control was free of these active components, which were almost totally replaced by water (**Table I**). The test formulation and vehicle control were supplied in a neutral, identical package, labelled by the manufacturer. As both formulations were based on identical w/o emulsions containing an additional amount of 14% lipids, they were comparable with regard to cosmetic properties and viscosity (4,050 and 3,400 mPas, respectively), assessed by Rheomat R123 (proRheo GmbH, Althengstett, Germany). The use of other skin care products or topical medications in the test area was not allowed for the entire duration of the study.

The topical steroids applied in the test area and discontinued prior to inclusion because the volunteer had entered a stage of clinical remission were as follows: hydrocortisone (7.7% of the volunteers; $n=2$), prednicarbate (19.2%; $n=5$), methylprednisolone aceponate (50.0%; $n=13$), and mometasone furoate (23.1%; $n=6$). For each volunteer the same topical steroid had been applied on both forearms/arms before entering the study. The protocol was approved by the ethics committee of the University of Lübeck (number 13-282). The study was performed according to the principles of the Declaration of Helsinki and all participants gave written informed consent beforehand.

Outcomes and assessment

The primary outcome was set as the number of arms on which a relapse, defined as "recurrent erythema on at least 1 arm for 3 consecutive days", occurred. For this purpose, the volunteers were asked to record the presence/absence of erythema on their left and right forearms/arms once daily in a diary using a standardized 0–3 scale (0=no visible erythema; 1=mild erythema; 2=moderately severe erythema; 3=severe erythema) and instructed to contact the study centre if manifest erythema on either arm, as described, had been noted. All participants who reported recurrent erythema persistent on 3 consecutive days were invited for an unscheduled visit to the study centre for assessment of their skin condition in the test area and check the diary by the investigator to confirm the relapse. All unscheduled visits took place within a minimum of 24 h (1 day) and maximum of 72 h (3 days) after the study centre had been informed about the relapse.

The secondary outcomes included the local SCORAD, the itch intensity in the test area, transepidermal water loss (TEWL), SC hydration and the amount of used test and vehicle control sample. The outcome parameters were assessed at baseline (D0) and at days 7 (D7), 14 (D14), 28 (D28), 56 (D56) and 84 (D84) or at the time of relapse (in case relapse before D84 occurred). Based on the timeline, the end of the study was defined as the time of relapse or D84, whichever occurred earlier. Compliance was documented at each visit to the study centre by the study personnel, and the correct application of the test and control samples, respectively amounts used, were checked by weighing the samples at the same time-points.

Clinical severity scoring and itch severity assessment

Clinical severity scoring was performed by assessment of the SCORAD intensity parameters in the test area (local SCORAD) taking into consideration the presence of erythema, exudation, papulation, excoriations, lichenification and skin dryness on a 0–3 scale (22). In addition, standardized photographs of both arms/forearms were taken at each study visit. The itch intensity in the test area was assessed by the volunteers by means of a visual analogue scale (VAS) from 0 (no perceptible itch) to 10 (worst imaginable itch).

Non-invasive assessment of the skin barrier function

Non-invasive assessment of the epidermal barrier function was performed by measurements of TEWL and SC hydration in clinically uninvolved and lesional skin areas on the volar surface of the forearms/arms. TEWL was measured with the open chamber system (Tewameter TM300) and skin hydration was assessed by measuring capacitance (Corneometer CM825), both devices from Courage and Khazaka Electronics (Cologne, Germany). The assessment of TEWL was based on the mean value of 3 consecutive measurements per field performed by the same investigator; the assessment of skin hydration was based on the mean value of 5 consecutive measurements per field. All measurements were performed under controlled environmental conditions (room temperature 20 ± 1°C; average relative humidity 40–45%) and according to the published guidelines (23–25). The volunteers were instructed not to apply water, any cleansing product, as well as the test and vehicle formulations, within 6 h preceding the measurements. In case of unscheduled visit, the volunteers received instructions by phone at the time they contacted the study centre to report a relapse, and compliance was checked by the investigator before final assessments of the barrier function had been performed.

Statistical analysis

Statistical analysis was performed using GraphPrism 5.0 (GraphPad Inc., San Diego, CA, USA). A p-value <0.05 was considered statistically significant. The primary outcome was analysed based on a comparison of the proportion of arms/forearms with recurrent inflammatory AD symptoms in the active formulation vs. control arm. Within each study arm, the changes in the secondary outcome parameters between baseline and the time of relapse were analysed by Wilcoxon signed-rank test. Differences in the measured para-

Table I. Active and vehicle formulation components

Active formulation (Eucerin® AtopiControl Body Lotion, Beiersdorf AG, Hamburg, Germany) components (INCI)
Aqua, glycerin, paraffinum liquidum, Vitis vinifera seed oil, Oenothera biennis oil, octyldodecanol, PEG-7 hydrogenated Castor oil, dimethicone, Glycyrrhiza inflata root extract, ceramide 3, tocopherol, ozokerite, sorbitane isostearate, methoxy PEG-22/dodecyl glycol copolymer, PEG-45/dodecyl glycol copolymer, PEG-2 hydrogenated Castor oil, hydrogenated Castor oil, ascorbyl palmitate, citric acid, sodium citrate, magnesium sulphate, butylated hydroxytoluene (BHT), 1,2-hexanediol, phenoxyethanol, potassium sorbate.
Vehicle formulation components (INCI)
Aqua, paraffinum liquidum, octyldodecanol, PEG-7 hydrogenated Castor oil, dimethicone, ozokerite, sorbitan isostearate, methoxy PEG-22/dodecyl glycol copolymer, PEG-45/dodecyl glycol copolymer, PEG-2 hydrogenated Castor oil, hydrogenated Castor oil, citric acid, sodium citrate, magnesium sulphate, 1,2-hexanediol, phenoxyethanol, potassium sorbate.

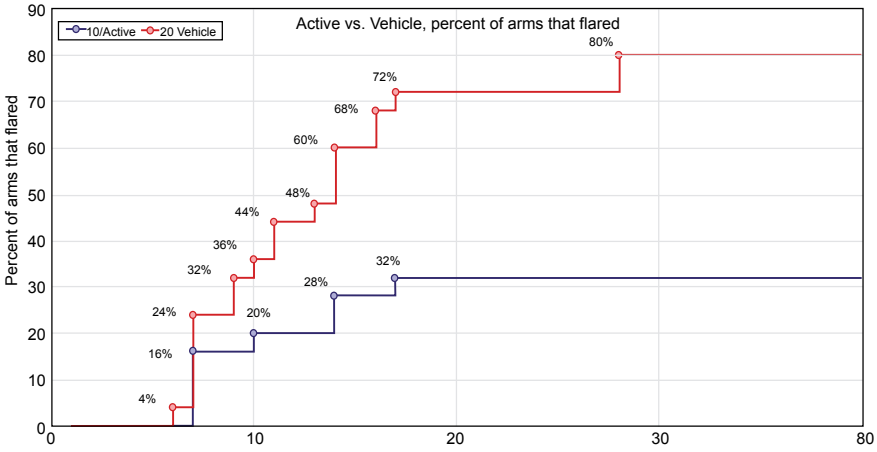

Fig. 2. Kaplan–Meier plot of relapses in the active formulation (*blue*) compared with vehicle arm (*red*) over time (data given as percentage of arms with atopic dermatitis flare).

meters between the active formulation and the vehicle arm at the time of relapse were analysed by Mann–Whitney test.

In the respective tables and figures, the values are expressed as mean and standard error (SEM), except for the clinical severity score and itch intensity, which are expressed as median and interquartile range.

RESULTS

Significantly reduced number of relapses in the active formulation compared with vehicle arm

Twenty-five of the randomized subjects completed the study per protocol. One patient was lost to follow-up from D28 onwards; consequently, the values documented on D14 were included in the data evaluation. Twenty-three patients (88.5%) experienced a relapse on at least one forearm/arm during the study period. The total number of forearms/arms on which a relapse occurred was 28, with 8 (28.6%) in the active formulation arm and 20 (71.4%) in the vehicle arm; the difference between the arms was significant ($p<0.01$) and corresponded to a 60% reduction in the relapse rate with the active formulation compared with the vehicle. The development of relapses over time is shown in **Fig. 2**.

The total amount of used test sample throughout the study was 1,108.36 g and 1,180.50 g for the active formulation and vehicle arm, respectively. The mean amount of test sample used per participant per arm was 46.18 g (active formulation) and 49.19 g (vehicle control); the differences between the arms were not significant.

Significant differences in the clinical and itch severity score between the study arms at time of relapse

The clinical severity score (local SCORAD), itch severity, TEWL and SC hydration in the active formulation and the vehicle arm at baseline and at the time of relapse are shown in **Table II**.

At baseline there were no significant differences in the local SCORAD between the study arms. At the time of relapse, the median local SCORAD in the active formulation arm was not significantly increased compared with baseline; the differences in the local SCORAD in the vehicle arm in contrast, were significant ($p<0.001$; Table II and **Fig. 3**).

Comparison of the increase of the local SCORAD in each study arm at the time of relapse (end of the study), assessed as Δ-value compared with baseline, showed a significant difference between the active formulation and the vehicle-treated arm ($p<0.001$; **Fig. 4**a).

At the beginning of the study, there were no significant differences in itch severity between the active formulation and the vehicle arm. At the time of relapse, the differences in the itch severity in both study arms were significant compared with baseline (active formulation and vehicle arm respectively, $p<0.01$ and $p<0.001$). The

Table II. Clinical severity (local SCORing Atopic Dermatitis [SCORAD]), itch intensity (visual analogue scale 0–10), transepidermal water loss (TEWL) and stratum corneum hydration (capacitance) in the active formulation and the vehicle arm at baseline and at time of relapse ($n=26$)

	Active formulation		Vehicle	
Arm/parameter	Baseline	Time of relapse	Baseline	Time of relapse
Local SCORAD, median (interquartile range)	1.25 (0.38/2.13)	2.0 (1.0/4.0)	1.0 (0.38/2.63)	5.0 (4.0/6.0)***
Itch severity, median (interquartile range)	0.0 (0.0/0.0)	0.4 (0.0/2.0)**	0.0 (0.0/0.0)	3.5 (1.0/5.5)***
TEWL (g/m^2/h), mean±standard error of the mean				
Non-lesional skin	7.15±0.58	7.84±0.76	7.59±0.73	10.19±0.95**
Lesional skin	8.30±0.83	11.32±1.47*	8.89±0.90	18.36±1.75***
Capacitance (arbitrary units), mean±standard error of the mean				
Non-lesional skin	30.01±1.99	34.49±2.38	30.51±2.02	25.31±2.22*
Lesional skin	26.29±2.17	28.96±2.50	26.46±2.40	18.39±1.56**

Level of significance $p<0.05$, *$p<0.05$, **$p<0.01$, ***$p<0.001$.

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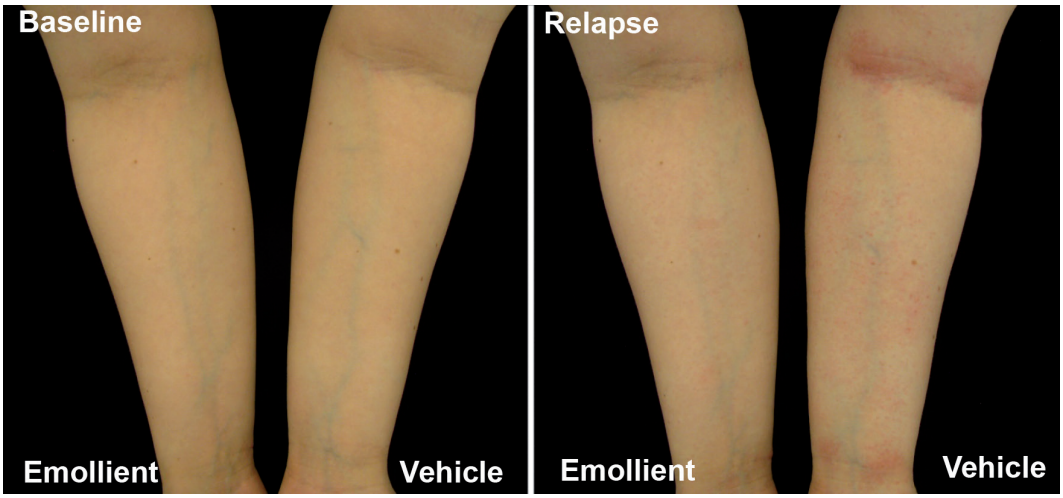

Fig. 3. Clinical photographs of the test areas (arms) treated with the active formulation (emollient) and vehicle at baseline and time of relapse.

increase in itch severity was more pronounced under treatment with the vehicle control and the difference in ΔVAS (itch severity) between the active formulation and the vehicle arm were significant ($p<0.001$; Fig. 4b).

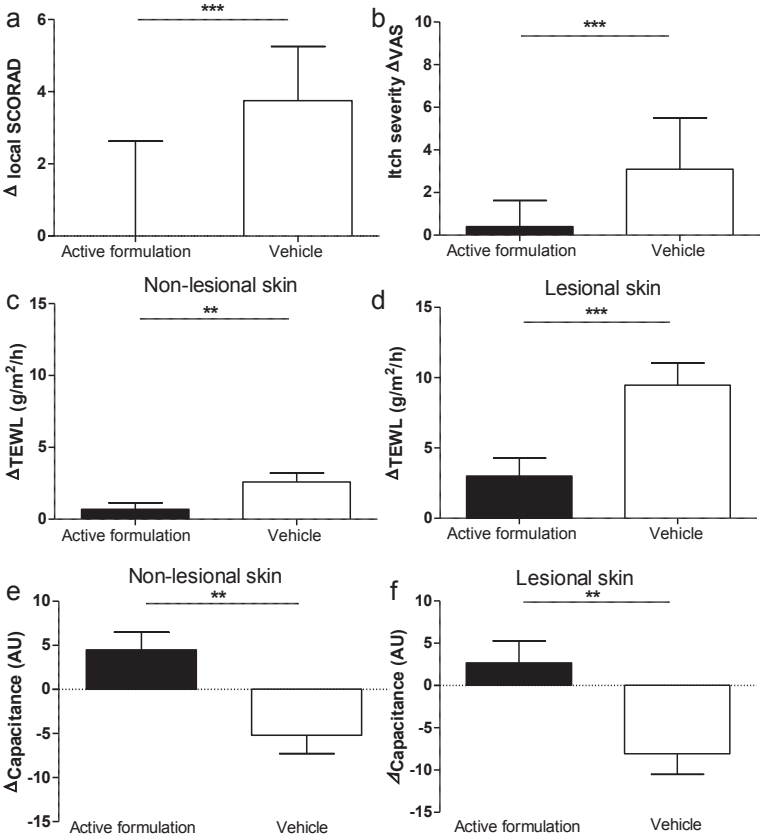

Fig. 4. Comparison of the changes in the lesional severity, itch intensity and skin barrier function between the active formulation and vehicle arm at the end of the study or time of relapse (DR) compared with baseline (D0): (a) local SCORing Atopic Dermatitis (SCORAD); (b) Itch severity; (c) transepidermal water loss (TEWL) non-lesional skin; (d) TEWL lesional skin; (e) Capacitance non-lesional skin; (f) Capacitance lesional skin. The data are presented as Δ-values (Δ=DR–D0) for the respective parameter; local SCORAD and itch severity: median and interquartile range; TEWL and capacitance: mean±standard error of the mean (SEM), n=26, level of significance $p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$. AU: arbitrary units.

Maintenance of the barrier homeostasis in the active formulation compared with vehicle arm

At baseline there were no significant differences in the mean TEWL values of the non-lesional and lesional skin between the arms. In the active formulation arm, the TEWL values of non-lesional skin at the time of relapse were not significantly higher than the baseline values, while on lesional skin the mean TEWL values increased significantly ($p<0.05$). In the vehicle arm the mean TEWL values of both non-lesional and lesional skin at the time of relapse were significantly higher than the baseline values ($p<0.01$ and $p<0.001$, respectively non-lesional and lesional skin; Table II). The comparison of the TEWL increase at the time of relapse (assessed as Δ-value compared with baseline) showed significantly higher ΔTEWL in the vehicle than in the active formulation arm (for ΔTEWL non-lesional and lesional skin, respectively, $p<0.01$ and $p<0.001$; Fig. 4 c, d).

Similarly to TEWL, there were no significant differences in the mean capacitance values measured on the non-lesional and lesional skin of the active formulation and vehicle arm at baseline. Application of the active formulation resulted in improvement of skin hydration and increased capacitance values at the end of the study/time of relapse compared with baseline (Table II). In contrast, at the time of relapse a significant decrease in capacitance was found on both the non-lesional ($p<0.05$) and lesional ($p<0.01$) skin of the vehicle arm. Furthermore, the differences in the capacitance changes (Δ-values) at the time of relapse between the active formulation and the vehicle arm were significant for both non-lesional and lesional skin (for both $p<0.01$; Fig. 4 e, f).

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DISCUSSION

The finding of the present study show that maintenance treatment with a w/o emollient containing licochalcone A, omega-6 fatty acids, ceramide 3 and glycerol as anti-inflammatory, barrier-strengthening and skin hydrating active components, led to a significantly reduced number of and risk of relapses after discontinuation of the topical steroid treatment in adult volunteers with mild to moderately severe AD. Although recent studies have shown benefits of emollient use for the prevention of flare, to the best of our knowledge a reduced risk of relapses by maintenance treatment with a non-prescription emollient, based on a randomized, double-blind study design, including comparison with the respective vehicle and excluding the use of concomitant medication has not been reported previously. As throughout the study there were no differences in the amounts of active formulation and vehicle control used, the intra-individual left–right comparison provides evidence that the reduced inflammatory activity, enhanced barrier function and SC hydration are attributed to the active components of the test formulation.

The anti-inflammatory properties of licochalcone A, a reversely constructed chalcone specific for the Xinjiang liquorice root *Glycyrrhiza inflata* have been characterized *in vitro* and shown to be directed towards suppressed release of pro-inflammatory mediators, such as prostaglandin E2 (PGE2), leukotriene B4 (LTB4), interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α) by the skin residential cells and the cells of the innate and adaptive immune system (26–29). The anti-inflammatory effects described *in vitro* have been confirmed by *in vivo* studies showing the efficacy of licochalcone A-containing skin care formulations in reducing experimentally-induced erythema and improvement of the inflammatory manifestations in patients with erythemato-telangiectatic rosacea and mild to moderately severe inflammatory forms of acne (30–32). Initial evidence for improvement of the symptoms of AD after emollient treatment with the w/o formulation used in the present study has been provided by the results of a controlled, randomized, investigator-blinded study showing significant reduction of SCORAD after 6-week, twice daily stand-alone application of the test formulation compared with 1% hydrocortisone (HC) in paediatric patients with mild to moderately severe eczema (33). These observations have been confirmed in an independent study that showed lack of significant differences in the percentage reduction of SCORAD after 1-week application of an oil in water formulation containing licochalcone A, compared with 1% HC in adult volunteers with mild to moderately severe, localized inflammatory lesions of AD (34).

Prevention of flares by controlled use of an emollient containing licochalcone A and oatmeal has been reported by Weber et al. (35). In a recent publication the authors found a significantly reduced number of flares along with prolonged time to flare in paediatric patients with AD, who were treated with a combination of the emollient and a mild cleansing body wash compared with body wash alone. The results of the present study confirm and extend these findings. Taken together, the significant differences in the number of arms in which a relapse occurred and the less pronounced clinical severity, i.e. significantly lower ΔSCORAD in the active formulation compared with vehicle arm at the time of relapse, provide first double-blind, vehicle-controlled evidence for reduced risk of flares by the use of the test formulation in the maintenance phase of AD.

In addition to the reduced risk of flare after discontinuation of the topical steroid treatment, the maintenance of the barrier function observed at the time of relapse in the non-lesional skin areas treated with the active formulation is a key finding of the present study. Compromised barrier function with increased baseline TEWL even in uninvolved skin areas is a major characteristic of AD and earlier studies in atopic skin have shown that TEWL is influenced by AD disease severity as well as inflammatory activity (36–40). In this regard, the lack of significant differences in the non-lesional skin TEWL in the active formulation arm and significantly increased TEWL at distant, i.e. non-lesional, skin areas in the vehicle arm at the time of relapse, provide evidence that the decreased disease activity shown by the reduced number of relapses translates into functional improvement and enhancement of the barrier function. In addition, the significant differences in the lesional skin TEWL increase (ΔTEWL) between the study arms at the time of relapse correlate to the less pronounced clinical severity, respectively significantly lower ΔSCORAD in the active formulation compared with the vehicle arm. Both evening primrose and grape-seed oil, contained in the active formulation, are rich sources of omega-6 fatty acids, specifically linoleic acid. Essential fatty acids (EFA), in particular linoleic acid, have a critical role in the formation of covalently bound ceramides, whereas the amounts of covalently bound ceramides are known to correlate with the permeability barrier function and contribute to the maintenance of its homeostasis (41–44). Atopic skin is characterized by decreased amounts of ceramide 1/linoleate and hence, several studies in the past investigated the effects of topical application of EFA-rich emollients in atopic individuals (45, 46). In a double-blind, placebo-controlled left-right comparison study, Anstey et al. observed improvement in the clinical signs of flexural eczema in atopic patients treated with a w/o emulsion containing evening primrose oil as an active ingredient compared with an active-free formulation (47). Janossy et al. showed *in vivo* enhancement of the barrier function in atopic skin as the result of topical application of a w/o emulsion containing 12.5% evening primrose oil compared with non-treatment (48). The differences in the barrier-strengthening effects of evening primrose

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oil as a function of the vehicle have been demonstrated in an *in vivo* human skin study by Gehring et al. showing significantly decreased TEWL after 4-week application of a w/o emulsion containing 20% evening primrose oil and lack of measurable effect by the application of an amphiphilic oil in water formulation with the same active concentration (49). These findings have been supported by the results of Billmann-Eberwein et al., who showed that pre-treatment with EFA-rich emollients reduced the severity of the atopy patch reactions induced by both seasonal (grass pollen) and perennial (house dust mite) allergens in sensitized atopic individuals (50). Seasonal and perennial allergens are well-known environmental triggers of the flares in AD individuals with clinically relevant sensitization (4, 5). Though the present study did not aim to investigate the effects of the active formulation with regard to the underlying sensitization profile, our results and the causal link between the maintenance of the barrier integrity and the initiation of the inflammatory response in the skin, suggest a protective effect of the test formulation in terms of prevention of flares triggered by environmental factors.

The number of arms on which a relapse occurred was considered the primary outcome of the present study. The variations and methodological difficulties regarding the definition of flare, or relapse, have been the focus of systematic reviews and recent publications that have aimed to validate measures for long-term disease control in prospective interventions of AD (51–53). As the individual threshold and perceived need for treatment may vary and consequently, impact behaviour, we used a symptom-based definition that was comprehensible and easily captured by the participants, while reflecting the escalation of symptoms and increased inflammatory activity, in case a relapse occurred. The daily recording of symptoms, the lack of recall bias and the investigator-blinded documentation of the relapse at the time it occurred, combined with objective measurements of the barrier function, therefore provide a reliable source of patient-oriented and physician assessment data to substantiate the protective effects exerted by the emollient.

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Conflict of interest: IA-F has been principal investigator and speaker for Beiersdorf AG, Hamburg, Germany. FR, DR and AF are employees of Beiersdorf AG, Hamburg, Germany. CA and TW are employees of Beiersdorf Inc., Wilton, CT, USA.

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