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Ectoine-Containing Cream in the Treatment of Mild to Moderate Atopic Dermatitis: A Randomised, Comparator-Controlled, Intra-Individual Double-Blind, Multi-Center Trial

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Key Words
Atopic dermatitis · Osmolytes · Ectoine · Topical treatment

Abstract
Introduction: The natural cyclic tetrahydropyrimidine, ectoine, is a low-molecular, water-binding, organic osmolyte. Previously, topical application of ectoine to healthy human skin was shown to improve skin hydration as well as skin barrier function. ***Objectives:*** We therefore speculated that topical application of ectoine would be beneficial for patients with atopic dermatitis (AD), in which a genetically defined defect in skin barrier function is of major pathogenetic relevance. We assessed the efficacy of an ectoine-containing cream (EHK02–01) in the management of 65 patients with mild to moderate AD in a randomized, intra-individual, double-blind, multi-center trial, in which the efficacy of ectoine was compared to a nonsteroidal anti-inflammatory cream previously found to primarily act on skin barrier function and therefore with a comparable mode of action. ***Methods:*** Sixty-five patients with mild to moderate AD aged 18–65 years were enrolled. The patients applied EHK02–01 and the control cream on two symmetrical lesions twice daily for 28 days. At the beginning, after 7 and after 28 days, treated skin areas were assessed by modified, objective local SCORAD (Scoring Atopic Dermatitis) and IGA (Investigator's Global Assessment) as well as the patients' judgment of efficacy and their assessment of pruritus. ***Results:*** EHK02–01 was found to be very well tolerated. Even more important, efficacy of EHK02–01 treatment was equivalent to that achieved with the reference product. ***Conclusion:*** These results indicate that topical treatment with EHK02–01 may represent a novel option for the treatment of patients with AD.

Introduction

Atopic dermatitis (AD) is a highly pruritic, inflammatory skin disease, for which there is no curative therapy available. Disease management is thus limited to symptomatic relief. Recent pathogenetic concepts indicate that AD results from the interplay of genetically determined defects in skin barrier function and immunologic deteriorations including defects in the innate immune system as well as aberrant immunologic responses to allergens and microbial antigens. Management of patients with AD depends on the severity of the disease and incorporates measures to improve skin hydration, skin barrier function, pharmacological therapy and the identification and elimination of flare factors such as allergens and irritants. Accordingly, patients with AD have

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reduced skin barrier function and dry skin, and thus use of emollients is an integral part of the topical treatment of this chronic skin disease [1]. Although quite useful, emollient therapy rarely leads to complete resolution of skin lesions, especially in severe cases. In particular, anti-inflammatory and immunomodulatory therapies are often required to treat acute flares of patients with moderate to severe AD. Since the introduction of topical corticosteroids, they have formed the principal cornerstones of anti-inflammatory therapy in AD [2]. More recently, topical calcineurin inhibitors have been introduced as an alternative, as they provide targeted anti-inflammatory activity without the local or systemic side effects seen with topical corticosteroids [3–5]. Although effective, unrestricted and long-term use of glucocorticosteroids and calcineurin inhibitors is hampered by the occurrence of unwanted side effects [reviewed in 6], indicating the need for alternatives. In this context, we and others have recently provided increasing evidence that the naturally occurring osmolyte, ectoine, may represent a promising therapeutic option. Ectoine is a low-molecular, cyclic tetrahydropyrimidine organic osmolyte, which was first identified by Galinski et al. [7] in the halophilic bacterium, *Ectothiorhodospira halochloris*, but has since then been found in a wide range of halophilic and halotolerant bacteria. Extremophilic microorganisms confer resistance towards damage by external stress. To protect themselves, they produce stress-protection molecules, the so-called extremolytes. Ectoine belongs to the class of compatible solutes and represents one of the most comprehensively investigated extremolytes which, in bacteria, serve as an osmoprotectant and stabilizer of cells and biomolecules [7, 8] to counteract extreme situations like osmotic stress, heat or desiccation [9]. In an attempt to transfer these protective properties of ectoine to human skin, ectoine has been used in skincare cosmetics for more than 10 years [10], and several studies have demonstrated the positive effects of ectoine on human skin [11, 12]. In particular, the application of a cosmetic emulsion containing different concentrations of ectoine has been shown to protect the skin barrier against water loss and to prolong skin moisture maintenance [10]. Our goal was to investigate the effect of an ectoine-containing cream (EHK02–01) in the management of patients with mild to moderate AD after topical application in vivo. For this purpose, we conducted a study in which the efficacy of EHK02–01 was compared to that achieved by treatment with MAS063DP (Atopiclair™). MAS063DP is the first medical device approved by the US Food and Drug Administration for relief of symptoms (itch, burning and pain) of AD and allergic contact dermatitis [13]. It is thought to act primarily by improving skin barrier function, and its efficacy has been well established in a number of recently conducted clinical trials [14–18] which demonstrate its efficacy and safety in mild to moderate forms of AD. We therefore chose this substance as the comparator in our trial. For the purpose of the study, MAS063DP will be referred to as the positive control throughout the manuscript.

Materials and Methods

Materials

EHK02–01 and the control product were provided by bitop AG, Witten, Germany, in identical, blinded containers. Each container was labeled with the participant's study number, and participants, observers and all trial personnel were blinded to the study treatment. EHK02–01 consisted of the following substances: ectoine, aqua, hydrogenated lecithin, ceramide-3, squalane, *Olea europaea* oil, caprylic/capric triglyceride, *Butyrospermum parkii* butter, *Oryza sativa* (rice) Bran Cera (a wax obtained from *O. sativa*), carbomer, xanthan gum, sodium carbomer, *Cardiospermum halicacabum* flower/leaf/vine extract, glycine, alanine, pentylene glycol, butylene glycol, hydroxyethylcellulose, glycerine and hydroxyphenyl propamidobenzoic acid. The positive control consisted of the following substances: aqua, ethylhexyl palmitate, *Butyrospermum parkii*, pentylene glycol, arachidyl alcohol, behanyl alcohol, arachidyl glucoside, glyceryl stearate, PEG-100 stearate, butylene glycol, glycyrrhetinic acid, capryloyl glycine, bisabolol, tocopheryl acetate, carbomer, ethylhexylglycerin, piroctone olamine, sodium hydroxide, allantoin, DMDM hydantoin, *Vitis vinifera*, sodium hyaluronate, disodium EDTA, ascorbyl tetraisopalmitate, propyl gallate and telmestein.

Patients

Patients were eligible for enrolment if they were male or female patients aged 18–65 years, with a diagnosed AD for ≥6 months, in the active stage, defined as an IGA score ≥1 and ≤4, and at least two comparable areas of AD on bilateral symmetric corresponding sides of the body, each of an area of at least 10 cm^2, with a modified, objective local SCORAD (Scoring Atopic Dermatitis) of >5 for both test areas. Both lesional areas of interest had to have a difference in the modified, objective local SCORAD of ≤3. Subjects were in general good health according to their medical history and a physical examination, and were excluded if there was any evidence of a skin disease or any other disease that, in the opinion of the investigator, would have affected the study objectives or safety of the subjects. Female participants were required to have negative pregnancy test at baseline, and to use a medically acceptable form of contraception throughout the trial. Subjects were also required to adhere to specific washout periods for a number of medications both prior to initiation of the study and throughout the study, including topical treatments of calcineurin inhibitors, corticosteroids or antibiotics (2 weeks) as well as systemic treatment with antihistamines (2 weeks), biologics (6 months), corticosteroids, antibiotics, immunosuppressive drugs or UV therapy (4 weeks). Volunteers were recruited in Germany

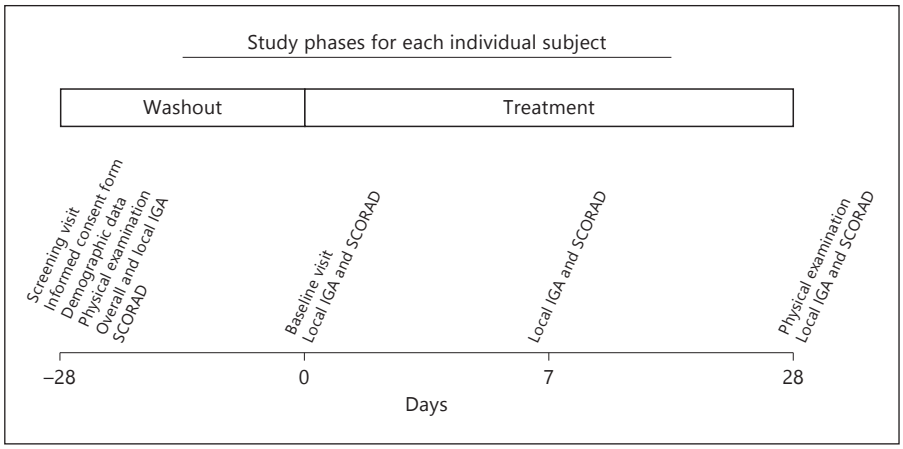

Fig. 1. Study design. The clinical investigation comprised 2 periods and 4 visits. During the 1st visit, demographic data were obtained and a physical examination was performed. After a washout phase of 28 days (period 1), all patients were supplied with the study investigational devices. At the beginning, and after 7 and 28 days, tested skin areas were assessed.

(Potsdam, Freiburg, Berlin and Mahlow) from four dermatologic practices. Approval had been obtained from a properly constituted independent ethics committee, the Freiburger Ethikkommission, Freiburg, Germany. The investigation was conducted according to the ethical rules stated in the Declaration of Helsinki Principles and the ICH-GCP guidelines (CPMP/ICH/135/95) and adhered to ISO 14155 as applicable. The clinical investigation was conducted in compliance with the German Medical Device Act (MPG § 20–22) and was registered on Clinicaltrials.gov (registration identifier NCT01079897). All patients gave written informed consent before enrolment.

Randomization and Treatment

After the inclusion and exclusion criteria had been checked on visit 2 (V2) on day 0, the patients were randomized to one of the two therapy arms A or B on the basis of a randomization list (A: left side = EHK02–01 and right side = positive control. B: left side = positive control and right side = EHK02–01). The randomization code and the corresponding emergency envelopes were compiled by a biometrician who was not otherwise involved in this clinical study. Randomization was carried out in blocks, on the basis of the internal randomization standard operating procedures to ensure balanced numbers of patients for each therapy group within the study centers. The size of the blocks was not indicated in the study protocol and the investigators were not notified thereof. A list of correlative patient numbers (1–120) was created. A random number (0–0.99) was generated for each patient number using the Excel function RAND (ZUFALLSZAHL). Patient numbers were assigned to therapy group A if the random number was greater than 0.5, otherwise to group B. Half of the blocks had their therapy group automatically assigned to be the complementary of the randomized blocks to assure an even distribution of treatment groups. The test area on each side was marked with a skin-marking pen before treatment. Treatment was performed twice daily, in the morning and in the evening, by the patients themselves, starting at day 0 (V2) and ending at day 28 (V4). Treatments were applied to both left and right extremities. No concomitant treatments or cosmetics were allowed on the selected test areas during the course of the investigation. The use of emollients and topical corticosteroids (class I or II) on any other AD lesions on ≤10% of the body surface was allowed.

Table 1. SCORAD

Criteria	Intensity
Erythema	0–3
Edema/papules	0–3
Oozing/crusts	0–3
Excoriation	0–3
Lichenfication	0–3

Study Design

Figure 1 illustrates the study design. During the first visit, demographic data were obtained and a physical examination was performed comprising a description of the general appearance and the measurement of height, weight, temperature, blood pressure and heart rate. The clinical investigation comprised 2 periods and 4 visits. After a washout phase of 28 days (period 1), all volunteers were supplied with the study medications. Tested skin areas were assessed at the beginning and after 7 and 28 days, as described below.

Efficacy

The primary objective of the study was to gain evidence of the efficacy of EHK02–01 as assessed by changes according to a modified, objective (local) SCORAD [19, 20] of the lesional area between V2 and V4. The scores of 5 clinical features (erythema, edema/papules, oozing/crusts, excoriation and lichenification) for one lesion were summed, resulting in a score ranging from 0–15 as shown in table 1. The SCORAD was evaluated at V2, V3 and V4 on both skin test areas. The secondary objectives were to evaluate the lesions by changes according to the IGA, the patient's judgment of efficacy and the patient's assessment of pruritus after 7 and 28 days and changes in the local SCORAD after 7 days. The IGA scores the severity of the symptoms using the system illustrated in table 2. This score takes into account the skin condition of the whole body (overall IGA) and the severity of the symptoms for the two test areas (local IGA). The patient rated the study medication and its tolerability (e.g. burning, stinging and tightness of skin) at V3 and V4 using the patient's judgment of efficacy on a 4-point

Table 2. IGA

0	Clear	No inflammatory signs of AD
1	Almost clear	Just perceptible erythema and just perceptible papulation/infiltration
2	Mild	Mild erythema and mild papulation/infiltration
3	Moderate	Moderate erythema and moderate papulation/infiltration
4	Severe	Severe erythema and severe papulation/infiltration
5	Very severe	Very severe erythema and very severe papulation/infiltration with oozing/crusting

Intensity: 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

Table 3. Patient's judgment of efficacy

Rating	Qualification
1	Did not help
2	Helped slightly
3	Quite good
4	Very good

Table 4. Size of test areas

	N	Mean	SD	Min	Median	Max
EHK02–01	65	62.52	50.18	12.00	42.00	247.00
Positive control	65	58.64	46.57	11.30	40.60	201.50

rating scale (1 = did not help, 2 = helped slightly, 3 = quite good and 4 = very good) (table 3). Pruritus was evaluated at V2, V3 and V4 on both test areas using a visual analog scale ranging from 0 to 10 cm (0 = no pruritus and 10 = worst pruritus). All skin assessments were performed by a trained dermatologist.

Safety Evaluation

Safety was evaluated at the baseline visit and at V4 by measurement of vital signs, a physical examination and patients answering questions on tolerability, AD severity and the nature and frequency of adverse events (AEs) as well as their relationship to the investigational devices.

Statistical Analysis

Given the exploratory nature of the study, no formal sample size calculation was performed. A total number of 60 randomized patients seemed to be sufficient to answer the questions raised in this protocol. The analysis with respect to the primary end point was performed in a confirmatory sense. All analyses of the secondary end points were descriptive/exploratory in nature (using $\alpha = 0.05$ for each test carried out without α-adjustment for multiple testing). To compare observations, the asymptotic Wilcoxon test for 2 dependent samples testing for noninferiority as described by Wellek [21] was used. The noninferiority margin was set to 10%. The margin was defined based on statistical analysis of previous published studies, with positive-control clinical relevant superiority over placebo still being given. Furthermore, the margin was small enough to assure that the EHK02–01 was not substantially inferior to the reference product.

Results

A total of 65 subjects were randomized in this study. Four (6.2%) withdrew from the study at V3 due to reasons not related to the treatment. Major protocol violations were identified in 11 patients. Thus, the safety and intention-to-treat samples comprised 65 subjects and the per-protocolsample for evaluations comprised 54 subjects. A diagram of the participant flow is shown in figure 2. Demographic and baseline characteristics were similar between treatment groups. The age of the subjects ranged from 18.20 to 61.90 years with a mean age of 33.27 ± 12.76 years (SD); 46.15% were male and 53.85% were female. All were of Caucasian race and presented an active stage of AD as defined by an overall IGA score of ≥1 and ≤4, i.e. almost clear, mild, moderate or severe: 26.15% had an overall IGA score reflecting mild symptoms, 67.69% showed a moderate value and 6.15% displayed severe symptoms. The mean size of the test area for EHK02–01 application was 62.52 ± 50.18 cm^2, ranging from 12 to 247 cm^2 at V2; for the control product, this was 58.64 ± 46.57 cm^2 (range 11.30–40.60 cm^2) (table 4). Mean use of EHK02–01 was 20.00 ± 13.61 mg/day/cm^2 between V2 and V3 and 16.88 ± 14.74 mg/day/cm^2 between V3 and V4. Mean use of the positive control was 20.24 ± 14.09 mg/day/cm^2 between V2 and V3 and 16.75 ± 12.85 mg/day/cm^2 between V3 and V4. A use of less than 4 mg/day/cm^2 was defined as noncompliant, reflecting a major protocol violation and therefore regarded as not PP.

Efficacy

At baseline, the mean SCORAD sums of the two groups were comparable (Wilcoxon test: $p = 0.5480$). As shown in figure 3, when on treatment with EHK02–01, the mean SCORAD sum decreased from 7.51 ± 1.76 (baseline) to 5.32 ± 2.49 at V3 (Wilcoxon test between V2 and V3: $p < 0.0001$), and to 3.77 ± 3.01 at the final visit (Wilcoxon test between V2 and V4: $p < 0.0001$). On treat-

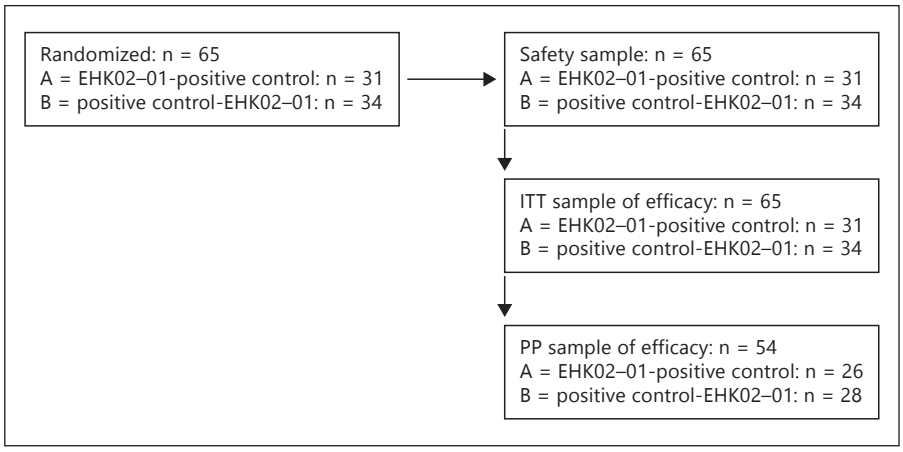

Fig. 2. Number of subjects per evaluation sample. A total of 65 subjects were randomized in this study. The safety and intention-to-treat (ITT) samples comprised 65 subjects and the per-protocol (PP) sample for evaluations comprised 54 subjects. Major protocol violations were identified in 11 patients.

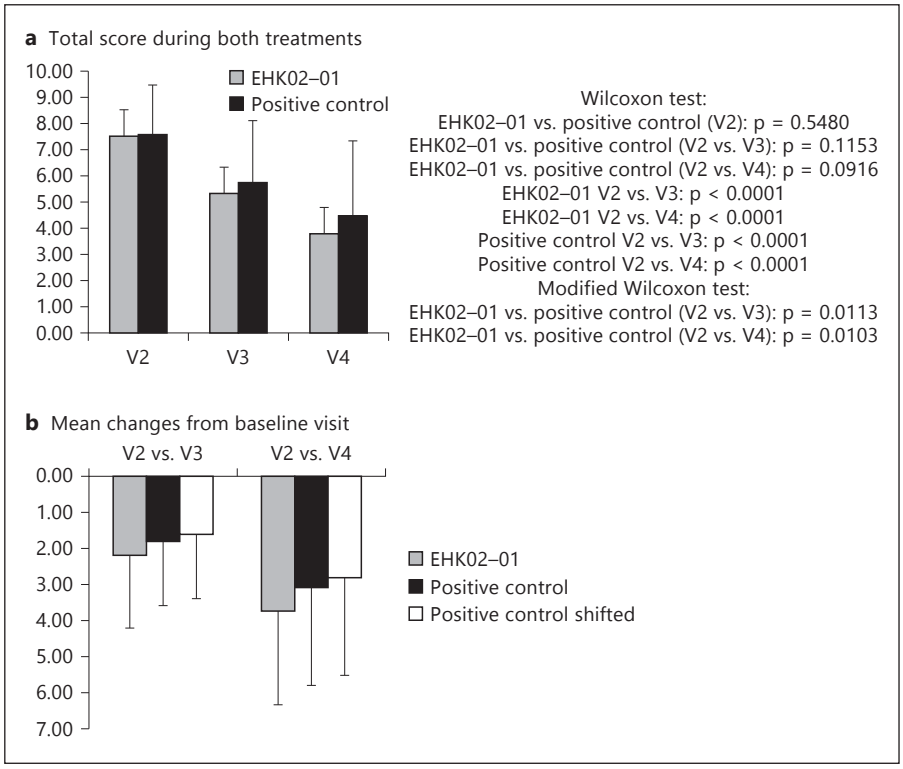

Fig. 3. SCORAD. **a** At baseline, the mean SCORAD sums for the EHK02–01 and the positive control treated area were comparable. On EHK02–01 treatment, the mean SCORAD sum decreased from 7.51 ± 1.76 (baseline) to 5.32 ± 2.49 at visit 3 ($p < 0.0001$), and to 3.77 ± 3.01 at the final visit ($p < 0.0001$). On treatment with the positive control, the mean SCORAD sum decreased from 7.55 ± 1.91 (baseline) to 5.74 ± 2.36 at visit 3 ($p < 0.0001$), and to 4.45 ± 2.88 at the final visit ($p < 0.0001$). The results of the Wilcoxon test were significant. **b** No significant differences in the mean SCORAD scores were seen when comparing both treatments with respect to the differences between V2 and V3 ($p = 0.1153$) and between V2 and V4 ($p = 0.0916$). For the modified Wilcoxon test, the distributions of the differences under the positive control were shifted and both modified Wilcoxon tests were significant ($p = 0.0113$ and $p = 0.0103$).

ment with the reference product, the mean SCORAD sum decreased from 7.55 ± 1.91 (baseline) to 5.74 ± 2.36 at V3 (Wilcoxon test between V2 and V3: $p < 0.0001$), and to 4.45 ± 2.88 at the final visit (Wilcoxon test between V2 and V4: $p < 0.0001$). No significant differences in the mean SCORAD scores were seen comparing both treatments with respect to the differences between V2 and V3 (Wilcoxon test between EHK02–01 and the control product: $p = 0.1153$) and between V2 and V4 (Wilcoxon test between EHK02–01 and the control product: $p = 0.0916$). For the modified Wilcoxon test, the distribution of the differences under positive control was shifted in the following way: because the median value of the differences between V2 and V3 was –2, a shift for –2·0.1 was performed, resulting in a mean shifted SCORAD sum of –1.62 ± 1.78. Similarly, as the median value of the differences between V2 and V4 was –3, a shift for –3·0.1 was performed, resulting in a mean shifted SCORAD sum of

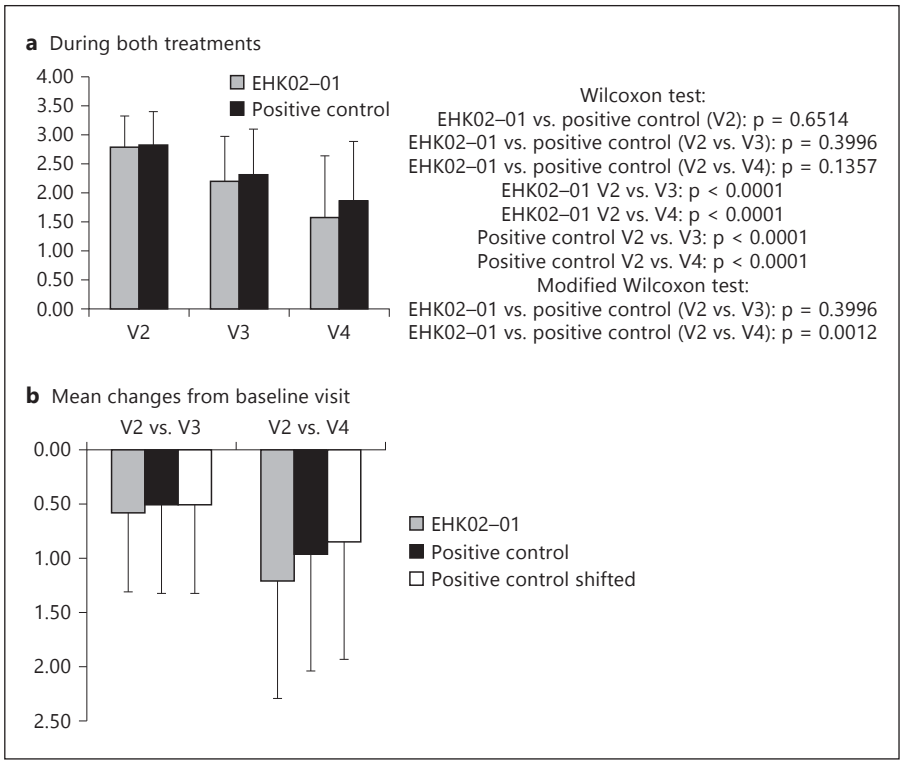

Fig. 4. IGA. **a** At baseline, the mean IGA scores for EHK02–01 and the positive control were comparable. On EHK02–01 treatment, the mean IGA scores decreased from 2.78 ± 0.54 to 2.20 ± 0.77 at visit 3 ($p < 0.0001$), and to 1.57 ± 1.07 ($p < 0.0001$) at the final visit: the mean decrease between V2 and V4 was 1.22 ± 1.08. On treatment with the positive control, the mean IGA score decreased to 2.31 ± 0.79 at visit V3 ($p < 0.0001$) and to 1.86 ± 1.03 at the final visit ($p < 0.0001$). The Wilcoxon test results were significant. **b** No significant differences in the mean IGA scores were seen comparing both treatments with respect to the differences between V2 and V3 ($p = 0.3996$) and the differences between V2 and V4 ($p = 0.1357$). For the modified Wilcoxon test, the distributions of the differences under positive control were shifted and the test with respect to V4 was significant ($p = 0.0012$), while the corresponding test with respect to V3 was not significant ($p = 0.3996$).

–2.81 ± 2.70. Both modified Wilcoxon tests were then significant with $p = 0.0113$ and $p = 0.0103$ showing the noninferiority of EHK02–01 with respect to the SCORAD score. In addition, the percentage change of the SCORAD total score between V2, V3 and V4, respectively, was determined for each patient and treatment. At the final visit, 35.38% of the patients had an improvement of 50 up to 75% and 27.69% had an improvement of 75 up to 100% on treatment with EHK02–01.

Investigator's Global Assessment

See figure 4. At baseline, the mean IGA scores for both study products were comparable (EHK02–01: 2.78 ± 0.54 and positive control: 2.82 ± 0.58; Wilcoxon test between treatments: $p = 0.6514$). On EHK02–01 treatment, the mean IGA scores decreased by 0.58 ± 0.73 points to 2.20 ± 0.77 at V3 (Wilcoxon test between V2 and V3: $p < 0.0001$), and to 1.57 ± 1.07 at the final visit; thus, the mean decrease between V2 and V4 was 1.22 ± 1.08 (Wilcoxon test between V2 and V4: $p < 0.0001$). On treatment with the control product, the mean IGA score decreased by 0.51 ± 0.81 points to 2.31 ± 0.79 at V3 and to 1.86 ± 1.03 at the final visit (Wilcoxon test between V2 and V3 and between V2 and V4: $p < 0.0001$). No significant differences in the mean IGA scores were seen comparing both treatments with respect to the differences between V2 and V3 (normal Wilcoxon test between treatments: $p = 0.3996$) and the differences between V2 and V4 (EHK02–01: –1.22 ± 1.08 and positive control: –0.95 ± 1.08; normal Wilcoxon test between treatments: $p = 0.1357$). The modified Wilcoxon test with respect to V4 was significant ($p = 0.0012$), while the corresponding test with respect to V3 was not ($p = 0.3996$), indicating that EHK02–01 showed noninferiority to the control product with respect to IGA score at V4. At V4, 44.62% of the patients had an IGA severity assessment of clear or almost clear after EHK02–01 treatment and 35.39% had this after treatment with the reference product.

Patient's Assessment of Pruritus

See figure 5. Pruritus was rated using a visual analog scale ranging from 0 to 10 cm (0 = no pruritus and 10 = worst pruritus). At baseline, the mean pruritus for the two different groups was not significantly different (EHK02–01: 46.78 ± 23.54 mm and positive control: 47.72 ± 25.12 mm; Wilcoxon test between treatments: $p = 0.9556$). On treatment with EHK02–01, the mean pruritus decreased by 22.69 ± 26.64 mm to 24.09 ± 22.17 at V3 (Wilcoxon test between V2 and V3: $p < 0.0001$), and to 22.80 ± 22.85 at

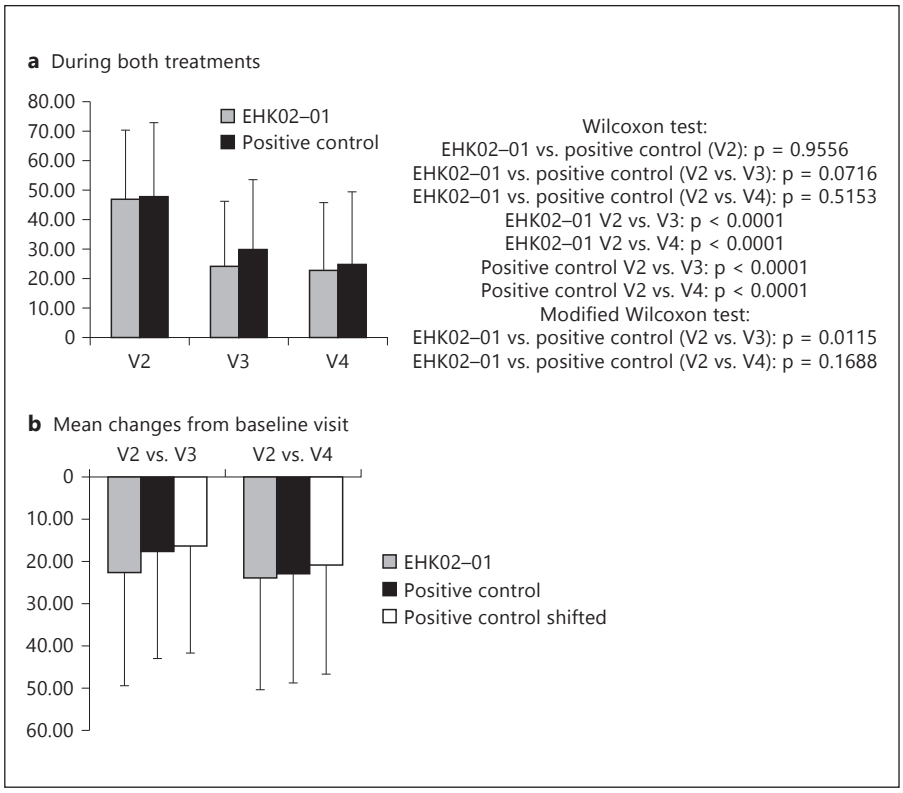

Fig. 5. Patient's assessment of pruritus. **a** At baseline, the mean pruritus for the area treated with EHK02–01or positive control was similar (EHK02–01: 46.78 ± 23.54 mm and positive control: 47.72 ± 25.12 mm). On EHK02–01 treatment, the mean pruritus decreased by 22.69 ± 26.64 mm to 24.09 ± 22.17 at visit 3 ($p < 0.0001$), and to 22.80 ± 22.85 mm at the final visit ($p < 0.0001$): the mean decrease between V2 and V4 was 22.98 ± 26.39 mm. on treatment with the positive control, the mean pruritus decreased to 29.98 ± 23.61 at visit V3 ($p < 0.0001$) and to 24.80 ± 24.66 at the final visit ($p < 0.0001$). **b** No significant differences in the mean pruritus were seen comparing both treatments with respect to the differences between V2 and V3 (EHK02–01: –22.69 ± 26.64 and positive control: –17.74 ± 25.30; $p = 0.0716$) and the differences between V2 and V4 (EHK02–01: –23.98 ± 26.39 and positive control: 22.92 ± 25.87; $p = 0.5153$) by means of the normal Wilcoxon test. The modified Wilcoxon test with respect to V3 was significant ($p = 0.0115$), while the corresponding test with respect to V4 was not significant ($p = 0.1688$).

the final visit; the mean decrease between V2 and V4 was 22.98 ± 26.39 (Wilcoxon test between V2 and V4: $p < 0.0001$). On treatment with the control product, the mean pruritus rating decreased to 29.98 ± 23.61 at V3 and to 24.80 ± 24.66 at the final visit (Wilcoxon test between V2 and V3 and between V2 and V4: $p < 0.0001$). No significant differences in the mean pruritus rating were seen comparing both treatments with respect to differences between V2 and V3 (EHK02–01: –22.69 ± 26.64 and positive control: –17.74 ± 25.30; $p = 0.0716$) and differences between V2 and V4 (EHK02–01: –23.98 ± 26.39 and positive control: –22.92 ± 25.87; $p = 0.5153$) by means of the normal Wilcoxon test. The modified Wilcoxon test with respect to V3 was significant with $p = 0.0115$, while the corresponding test with respect to V4 was not ($p = 0.1688$).

Patient's Judgment of Efficacy

At V3 and V4, patients rated the study medication using the patient's judgment of efficacy. At V3, mean efficacy assessment was 2.58 ± 1.01 on EHK02–01 treatment and 2.38 ± 0.93 on treatment with the control product. At the final visit, EHK02–01 reached a mean efficacy assessment of 2.74 ± 0.92 and the control product had a value of 2.52 ± 1.09. No significant differences in the mean efficacy assessment were observed when comparing both treatments with respect to V3 and V4 by means of the normal Wilcoxon test (Wilcoxon test at V3: $p = 0.1506$ and at V4: $p = 0.0918$). Both modified Wilcoxon tests were significant ($p < 0.0001$), showing the noninferiority of the EHK02–01 treatment compared to the positive control.

Safety

Overall, both products were well tolerated with 8 AEs occurring in 6 subjects (9.2%) during the study. One patient experienced 3 AEs and all others experienced 1 only. Two of the AEs experienced were general symptoms (bronchitis and cold, respectively), 1 local AE (burning) was observed at both test areas, 2 local AEs were observed on EHK02–01 treatment and 3 on the control therapy. No specific AE description is available because these AEs were recorded in the course of the queries put to the patients, based on a tolerability judgment of 'very bad' or 'bad'. At V3 and V4, the patients were asked to assess the tolerability and safety of both treatments on a 5-point rating scale (1 = very bad, 2 = bad, 3 = moderate, 4 = good and 5 = very good). There was only a very small number of patients who judged tolerability as very bad or bad (EHK02–01: at V3 n = 2, at V4 n = 1 and positive control:

at V3 n = 3, at V4 n = 1). Both treatments were well tolerated; no significant differences concerning tolerability were detected between the two treatments.

Discussion

In this randomized, comparator-controlled, intra-individual, double-blind, multi-center trial, we provide evidence that the topical application of EHK02–01 to lesional skin of patients with mild to moderate AD significantly reduced the clinical severity of the AD, regardless of whether it was measured by SCORAD, IGA or self-assessment. In addition, intra-individual comparison revealed that the therapeutic efficacy of EHK02–01 did not significantly differ from that achieved by treatment with the positive control, i.e. a medical device with established therapeutical efficacy for AD which is thought to act primarily by improving skin barrier function. This study thus corroborates and extends the previous notion that patients with AD benefit from the use of ectoine-containing skin products [10]. We are aware that our trial is limited by the lack of a placebo group. However, it is to be noted that the therapeutic effects achieved by EHK02–01 did not differ significantly from those obtained with the reference product, i.e. a product with well-established efficacy. As prescription treatments are often hampered with risks of unwanted side effects, and safety concerns regarding topical corticosteroid use exist, efforts have been made in recent years to minimize exposure to these substances and to develop new products. Due to the course of the disease, a multitherapeutic approach incorporating short-term management of acute symptoms and longer-term strategies to maintain optimal skin care is needed for the treatment of AD. The results obtained in our study together with the notion that topical application of ectoine to human skin has virtually no side effects [22–26] indicate that EHK02–01 may be ideal for long-term management of patients with AD. Our trial did not assess the mode of action of ectoine in AD. Previous studies have shown that ectoine protects the skin barrier against water loss, increases skin hydration and has a long-lasting moisturizing effect on the skin [10], indicating that epidermal barrier function represents a potential therapeutic target for ectoine. Furthermore, ectoine was shown to stabilize the cell membrane structures of human epithelial cells, including epidermal keratinocytes, and to thereby prevent the initiation of proinflammatory signaling cascades, including mitogenactivated kinases, which are required for the upregulation of inflammatory molecules such as intercellular adhesion molecule-1 (ICAM) on the surface of human keratinocytes [27]. This adhesion molecule is a hallmark of inflammatory skin diseases such as psoriasis and AD [28]. In animal experiments, ectoine has also been found to protect against nanoparticle-induced neutrophilic lung inflammation, regardless of whether it is given with or before the nanoparticle [29, 30]. Taken together, these studies strongly indicate that ectoine has anti-inflammatory properties. In aggregate, ectoine-containing products may represent a novel treatment option for mild to moderate forms of AD. Considering the well-documented fact that compatible solutes in general and ectoine in particular are characterized by an extremely high biocompatibility and almost completely lack side effects [8], we propose that ectoine-containing preparations are ideally suited for the long-term management of patients with AD. Concerning the current treatment algorithm of AD, we envision that ectoine could be placed as a standard therapy between emollients and specific anti-inflammatory compounds such as topical corticosteroids or topical calcineurin inhibitors. Our observations will hopefully prompt further studies to more closely evaluate the therapeutic potential of EHK02–01 in larger clinical trials for AD and other inflammatory skin diseases which are characterized by a defect in skin barrier function.

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