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Abstract

Background The aim of the controlled double-blind trial was to demonstrate the superiority of a topical combination product over its single constituents.

Patients and Methods A total of 278 patients with atopic dermatitis were randomized into four groups: 79 patients were treated with a topical combination of levomenol and heparin (A), 80 patients with levomenol alone (B), 78 patients with heparin alone (C) and 41 patients with the cream base with no active substances (D). The medication was applied twice daily for 8 weeks. Efficacy criteria included the severity of pruritus (visual analogue scale, VAS) and the SCORing Atopic Dermatitis (SCORAD) index as well as the overall assessment of efficacy and tolerance by both physician and patient.

Results The improvement of pruritus and SCORAD values in Group A was significantly higher compared with Groups B–D (ANOVA, P < 7 × 10^{-5}). The improvement of pruritus in Group A approximately corresponded to the cumulative effect of the two single active substances, with mean improvements of itching of −41.3, −13.3, −21.3 and +0.6 mm VAS in Groups A–D, respectively (95% CI 7.1–13.5, 2.9–9.2 and 10.4–18.3 mm for the comparisons A vs. B, A vs. C and A vs. D).

Conclusion The combination of levomenol and heparin proved to be significantly more efficacious in the treatment of pruritus and inflamed skin than the preparations of the single components.

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Keywords
(−)-α-bisabolol, atopic dermatitis, combination justification, heparin, levomenol

Conflict of interest

This clinical study was supported by funds from Harras Pharma, the marketing authorization holder of the study medication. The sponsor was, however, not involved in the planning, execution, evaluation and publication of the clinical trial. These tasks were carried out under the responsibility of the principal investigator.

Introduction

Topical preparations for the treatment of eczema and pruritus with dry skin should possess anti-inflammatory and possibly also anti-allergic and anti-pruritic action and have good tolerance in long-term use. Corresponding preparations based on levomenol and heparin are available as officially authorized medicinal products in the Czech Republic, with a long history of clinical use.

Levomenol, also called (−)-α-bisabolol, is present in, among other plants, the essential oil of chamomile. This plant metabolite possess pronounced anti-inflammatory and healing effects when applied topically. It is therefore a common constituent of skin care products, e.g. in topical preparations for the treatment of allergic skin conditions.

Heparin has likewise been shown to have anti-inflammatory, anti-allergic and wound healing properties. It has been applied for the topical treatment of eczema. The histamine-binding effect of heparin in vitro and in vivo potentially contributes to the clinical anti-allergic effects, as histamine and its physiological derivatives have been shown to be responsible for itching. The anti-inflammatory activity of heparin is clearly distinct from the anti-coagulant mechanisms of action evident from systemic application.
Positive effects in the prevention of acute episodes of atopic dermatitis were observed with a skin care lotion containing, *inter alia*, levomenol and bisabolol.\(^{50}\) In a previous double-blind clinical study of patients with atopic eczema and pruritus, we demonstrated the efficacy of a cream with a fixed combination of the two active ingredients vs. active-free cream base.\(^{10}\) The aim of this clinical study was to provide evidence for the contribution of the two individual active substances of the topical fixed combination product, as examined in our previous study, to the overall efficacy in the treatment of atopic dermatitis.

**Study design**

The four study preparations tested were based on the identical, cortisone-free cream base manufactured as an O/W emulsion (Group D) and differed in Groups A, B and C only by the addition of natural levomenol (0.3 g/100 g cream, Groups A and B) or heparin (20 000 IU/100 g cream, Groups A and C). The venum cream of Group A with levomenol and heparin corresponded to the medicinally authorized commercial cream Sencisutan\(^{8}\) (Harras Pharma Curarina, Munich, Germany; batch no. 1/0708). The four study preparations were produced by the same manufacturer (Ge
dlich's Pharmaceutische Extrakte GmbH, D-82547 Ersaburg, Germany) using the same validated manufacturing method for all four medications. The preparations did not differ in appearance, odour, viscosity or other organoleptic properties. The blinding of the preparation and the concealment of investigators to the patient’s individual study medication was guaranteed through the labelling provided by the manufacturer of the creams with the aid of the randomization list only available to the manufacturer until unblinding. According to Good Clinical Practice (GCP) rules, physicians, patients, the statistician and the study sponsor were fully blinded until statistical assessment was completed.

The clinical trial was designed as a prospective, randomized, reference-controlled, double-blind, two-centre and four-armed parallel group study. A case number calculation was made based on the values of the previous study,\(^{50}\) where significant superiority of the study medication vs. the cream base was found for itching, with a standardized difference of 1.195 score points. It was assumed that levomenol and heparin contribute to the overall efficacy in an additive manner and to a similar extent, i.e. between 40% and 60% each. Assuming similar standard deviations, standardized differences of 0.478 and 0.717 between the study medication (Group A) and the more and the less active component were expected, respectively. At \(\alpha = 0.05\) and an expected standardized difference of 0.478, the combination group and the two groups with the single constituents (Group B and C) would require 70 patients each (not accounting for dropouts) to obtain a power of \(1 - \beta = 0.80\). As the standardized difference between the combined cream and the treatment with the cream base is larger than that between the combination and the single substance drugs, the size of the cream base group was set to 35 patients. This number was higher than that obtained by the formal calculation; however, it is recommendable to confine an asymmetric group size to a minimum of 50% of the comparator group. To account for a dropout rate of approximately 10%, it was decided to include 80 patients into the active groups, and 40 in the cream base group (total of 280 patients).

A total of 280 patients with atopic dermatitis were screened. From this population, 278 participants were included in the study (intention-to-treat (ITT) population). According to the order of their entry into the study, the patients were allocated to the treatment groups according to a computer-generated blinded randomization list which ensured a patient distribution in the ratio of 2 : 2 : 2 : 1 in the four groups (Group A: \(n = 79\); Group B: \(n = 80\); Group C: \(n = 78\); Group D: \(n = 41\)). The corresponding medication was applied to the affected eczematous skin areas twice daily over a period of 8 weeks.

Inclusion and exclusion criteria were defined and complied with. Patients up to the age of 60 could be included. The use of systemic or topical corticosteroids, oral or topical immunosuppressants, anti-phlogistics, anti-depressants, anti-histamines, tar preparations, evening primrose oil, gamma-linolenic acid or psoralen plus ultraviolet A therapy was excluded within 1 week prior to screening and during the study. There was no specific inclusion criterion defined regarding the severity of the atopic dermatitis and no stratification by disease severity was made. No accompanying skin disease or a hypersensitivity to any of the cream ingredients was allowed to be present. The inclusion of children was explicitly approved by the Ethics Committee and the State Institute for Drug Control (SUKL).

**Vote of the Ethics Committee**

The study was planned and carried out in accordance with the criteria of GCP and the ethical standards defined in the declaration of Helsinki. The trial was registered under EudraCT No. 2005-002951-41. An approval of the Ethics Committees of the study centres and the Czech drug authorization authority (SUKL) as well as a signed informed consent form for all participants was obtained. In the case of children, a signed informed consent form of the parent or legal representative was obtained. The start of the trial (inclusion of the first patient) was on 31 August 2005 and the final visit of the last participant took place on 24 October 2007.

**Study duration and procedure**

At the start of the study, the demographic data (age, gender, height and weight) was collected and a complete medical history was obtained. As starting values for the study, the SCORing Atopic Dermatitis (SCORAD) index was determined. This index includes the percentage of the inflamed body surface (component A) and, on a scale from 0 (= absent) to 3 (= very severe), the degree of severity of the redening, swelling or rough skin, exfoliation, crust formation, scratch traces and the dryness of the non-inflamed skin area (component B). In addition, the degree of severity of pruritus and sleep disturbances caused by pruritus (component C) was
determined by means of a visual analogue scale (VAS). From these components, the index is calculated according to the formula \( A/5 + 7 \times B/2 + C \). For very young patients, the individual components were supplied by the legal representative.

The duration of the study was 8 weeks, with an interim visit after 4 weeks of treatment.

**Statistics**

SPSS v.16.0 was used as the statistical software (SPSS Inc., Chicago, IL, USA). The statistical analysis aimed at testing the three consecutive hypotheses in a closed test system. As a null-hypothesis, it was assumed that the effect of the combination group on pruritus was statistically not different from the effect of (in this sequence) the control group, the levomenol group and the heparin group. The evaluation was based on the documentation of the symptom of pruritus from component C of the SCORAD index. Missing values were to be replaced by carrying over the last recorded measurement.

All confirmatory analyses were performed in the ITT population by analysis of covariance (ANCOVA) with baseline values as covariate and the mean pre-post-difference as the dependent variable. Inter-group differences A vs. B, A vs. C and A vs. D were then tested using ANCOVA, adjusted for starting value. The adjustment leads to considerably smaller group differences than that derived from unadjusted VAS means. Adjusted ANCOVA analyses would therefore avoid overestimation of treatment differences. Every pair of hypotheses was tested at a two-sided significance level of 0.05, which maintains the overall significance level at \( P = 0.05 \).

Secondary (non-confirmatory) parameters were the statistical testing for the parameters of pruritus after 4 weeks (ANCOVA), the SCORAD index after 4 and 8 weeks (ANCOVA), and – using non-parametric tests (Mann–Whitney) and the \( t \)-test – the overall assessment of the efficacy by the physician by means of the VAS, the independent overall assessment of the efficacy by the patients (or their legal representatives) using a verbal rating scale (VRS with the five steps of no efficacy, low, moderate, good and very good) and the assessment of the overall tolerance by the patients on a five-step VAS (very poor, poor, moderate, good and very good). Undesired effects were to be documented and descriptively analysed.

**Results**

**Demographic data**

A total of 278 outpatients with an average age of 30.6 ± 16.3 years (0.7–59 years) and the diagnosis of atopic dermatitis were included in this study (ITT population; Fig. 1). The inclusion and exclusion criteria, which specifically refers to excluded co-medication, were met in all cases. A total of 101 patients were male and 177 female. After randomization, 79, 80, 78 and 41 patients were assigned to Groups A (combination), B (levomenol alone), C (heparin alone) and D (active agent-free cream) respectively (Table 1). Four patients prematurely discontinued participation in the study after the interim visit (week 4): one patient from Group C (poor compliance) and three patients from the control Group D (one for not returning, one at the request of the patient and one for poor compliance). The per protocol (PP) population therefore consisted of a total of 274 participants (79 in Group A, 80 in Group B, 77 in Group C and 38 in Group D).

Children and young people up to the age of 18 represented a substantial proportion of the study population. A total of 76 participants under 18 years of age (27.3%) were included in the study. The distribution according to age categories is shown in Table 1. The two youngest children (combination group) were 0.7 years old. For children up to the age of 12, a separate subgroup analysis was carried out.

The compliance of the application (assessed based on returned tubes of the study medication) proved to be good in all participants in the PP population.

**Primary efficacy parameter: pruritus**

The severity of pruritus was estimated on a 100-mm VAS. The itching decreased in treatment Groups A, B and C, and slightly worsened in Group D (control group) (Fig. 2; unadjusted values).
Table 1 Age distribution of the study participants

<table>
<thead>
<tr>
<th></th>
<th>Total n = 278</th>
<th>Lev + Hep Group A n = 79</th>
<th>Levomelol Group B n = 80</th>
<th>Heparin Group C n = 78</th>
<th>Cream base Group D n = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum</td>
<td>0.7 years</td>
<td>0.7 years</td>
<td>2 years</td>
<td>1 year</td>
<td>0.9 years</td>
</tr>
<tr>
<td>Maximum</td>
<td>59 years</td>
<td>59 years</td>
<td>59 years</td>
<td>59 years</td>
<td>59 years</td>
</tr>
<tr>
<td>0-6 years</td>
<td>18 (6.5%)</td>
<td>3 (3.8%)</td>
<td>4 (5.0%)</td>
<td>6 (7.7%)</td>
<td>5 (12.2%)</td>
</tr>
<tr>
<td>7-12 years</td>
<td>21 (7.6%)</td>
<td>6 (7.6%)</td>
<td>5 (6.3%)</td>
<td>8 (10.3%)</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>13-18 years</td>
<td>37 (13.3%)</td>
<td>8 (10.1%)</td>
<td>9 (11.3%)</td>
<td>13 (16.7%)</td>
<td>7 (17.1%)</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td>202 (72.7%)</td>
<td>62 (78.5%)</td>
<td>62 (77.5%)</td>
<td>51 (65.4%)</td>
<td>27 (65.9%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>177 (63.7%)</td>
<td>51 (64.6%)</td>
<td>56 (70.0%)</td>
<td>46 (59.0%)</td>
<td>24 (58.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>101 (36.3%)</td>
<td>28 (35.4%)</td>
<td>24 (30.0%)</td>
<td>32 (41.0%)</td>
<td>17 (41.5%)</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>24.1 ± 14.8 years (0.3-59 years)</td>
<td>25.1 ± 14.9 (0.5-59)</td>
<td>24.0 ± 13.3 (2.0-53)</td>
<td>23.1 ± 15.3 (0.3-55)</td>
<td>23.8 ± 16.2 (1.0-55)</td>
</tr>
</tbody>
</table>

Figure 2 Reduction of pruritus (in mm VAS) after 4 and 8 weeks of treatment (unadjusted values). P-values reflect intragroup differences to baseline (paired t-test). All intergroup comparisons were highly significant (analysis of covariance; P < 10⁻⁶ in all cases).

In the consecutive comparisons of treatment effects between Group A and all other groups (primary confirmatory parameter, three null-hypotheses tested according to the closed test principle) the relative effect in Group A was in all cases significantly superior. Statistical analysis of group differences was performed using ANCOVA in the ITT population after adjustment for equal baseline values, and confirmed the conclusion from the descriptive interpretation (Table 2; adjusted values). This calculation was also carried out in parallel for the PP population as a descriptive (non-confirmatory) evaluation, with comparable results (Table 2).

The sum of the intergroup differences for the individual substances in the confirmatory ITT analysis (week 4: ΔA vs. B = 10.3 mm VAS; ΔA vs. C = 6.0 mm; ΔA vs. ΔA; ΔA vs. ΔA; ΔA = 16.3 mm, week 8: ΔA vs. B = 15.9 mm VAS; ΔA vs. C = 9.7 mm; ΔA = 25.6 mm) results in an overall effect in the order of magnitude of the effect of the combination vs. control treatments (week 4: 14.4 mm VAS for A vs. D; week 8: 24.3 mm), and therefore confirms additive effects of the two individual substances.

The subgroup analysis of children up to the age of 12 years also showed a significant advantage of the combination treatment compared with the individual treatment and the cream base (A vs. B: P = 0.044, 95% CI 0.3-20.6 mm; A vs. C: P = 0.024, 95% CI 1.5-18.3 mm; A vs. D: P = 0.001, 95% CI 11.8-33.3 mm). The unadjusted mean improvement compared with the baseline value was 30.13 ± 2.95 mm on the VAS scale for the combined topicals, but that for the placebo arm was 7.39 ± 3.64 mm (B: 21.89 ± 3.18 mm; C: 22.17 ± 2.41 mm). No significant difference in the response to the respective study preparations resulted from the separate analysis of the patients aged from 0 to 6 years (n = 18) or 7 to 12 years (n = 21), although in all cases there was a tendency towards a more strongly pronounced effect in the group of 7-12-year-old children.
Table 2 Comparison of the adjusted outcome measures after 4 and/or 8 weeks of treatment: difference in effect of the combination Group A and Groups B-D

<table>
<thead>
<tr>
<th>Group comparison</th>
<th>Analysis</th>
<th>Mean difference</th>
<th>P-value (ANOVA)</th>
<th>95% CI (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus (VAS) (mm ± SD)</td>
<td></td>
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</tr>
<tr>
<td>A vs. B</td>
<td>Week 4</td>
<td>10.3 ± 1.6</td>
<td>2.2 × 10⁻⁹</td>
<td>7.1–13.5</td>
</tr>
<tr>
<td>ITT = PP</td>
<td>Week 8</td>
<td>15.9 ± 1.6</td>
<td>1.1 × 10⁻¹⁸</td>
<td>12.8–19.0</td>
</tr>
<tr>
<td>A vs. C</td>
<td>Week 4, ITT</td>
<td>6.0 ± 1.6</td>
<td>2.4 × 10⁻⁴</td>
<td>2.9–9.2</td>
</tr>
<tr>
<td></td>
<td>Week 8, ITT</td>
<td>9.7 ± 1.6</td>
<td>4.6 × 10⁻⁹</td>
<td>6.6–12.8</td>
</tr>
<tr>
<td></td>
<td>Week 8, PP</td>
<td>9.7 ± 1.6</td>
<td>6.9 × 10⁻⁹</td>
<td>6.5–12.8</td>
</tr>
<tr>
<td>A vs. D</td>
<td>Week 4, ITT</td>
<td>14.4 ± 2.0</td>
<td>9.7 × 10⁻¹¹</td>
<td>10.4–18.3</td>
</tr>
<tr>
<td></td>
<td>Week 8, ITT</td>
<td>24.3 ± 2.1</td>
<td>3.4 × 10⁻⁹</td>
<td>20.2–28.5</td>
</tr>
<tr>
<td></td>
<td>Week 8, PP</td>
<td>23.3 ± 2.0</td>
<td>4.2 × 10⁻¹¹</td>
<td>19.3–27.2</td>
</tr>
<tr>
<td>SCORAD (score points ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A vs. B</td>
<td>Week 8, ITT</td>
<td>9.4 ± 1.3</td>
<td>5.8 × 10⁻¹³</td>
<td>6.9–11.8</td>
</tr>
<tr>
<td>A vs. C</td>
<td>Week 8, ITT</td>
<td>6.7 ± 1.2</td>
<td>6.9 × 10⁻⁹</td>
<td>4.4–9.1</td>
</tr>
<tr>
<td>A vs. D</td>
<td>Week 8, ITT</td>
<td>14.6 ± 1.3</td>
<td>9.5 × 10⁻¹⁰</td>
<td>12.8–17.1</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat population; PP, per protocol population; SCORAD, SCORing Atopic Dermatitis; VAS, visual analogue scale.

SCORAD index

Improvements of the SCORAD index were observed in all groups. The largest improvement compared with the unadjusted starting value was again observed in the combination group followed by hepatin and levomenol groups, whereas the improvement in the control group was comparatively less pronounced (Fig. 3). The adjusted differences for each individual comparison of the combination group with the reference groups were statistically highly significant (Table 2).

In the subgroup analysis in children up to the age of 12 years, the effect on the SCORAD index was likewise highly significant (adjusted values A vs. B: P = 0.054, 95% CI –0.2 to 20.0; A vs. C: P = 0.003, 95% CI 4.5–19.4; A vs. D: P = 0.001, 95% CI 8.3–24.4). The treatment effect was not influenced by the age of the patients significantly (comparison 0–6 years vs. 7–12 years), although the group of 7–12 years showed a slight tendency towards better effects.

Overall assessment of the efficacy by patient and physician

The previously established group differences were confirmed in the assessment of the overall efficacy by the patients on a four-step VRS. At the end of the study, the treatment effect was assessed as good or very good by 97% of patients treated with the combination therapy, by 78% treated with hepatin alone, by 66% treated with levomenol alone and by only 41% treated with the cream base. Considering children from 0 to 12 years of age, the assessment as 'good' or 'very good' was made by 100% of the patients treated with the combination therapy, compared with 42.9% treated with the cream base (P = 0.002).

Figure 3 Effect on the SCORAD index after 4 and 8 weeks of treatment (unadjusted values). P-values reflect intragroup differences to baseline (paired t-test). All intergroup comparisons were highly significant (analysis of covariance; P < 10⁻¹⁰ in all cases).
The differences proved to be statistically highly significant already after 4 weeks and they continued to improve throughout the study period (Mann–Whitney test in the ITT population at time points 4 and 8 weeks: A vs. B: \( P = 1.91 \times 10^{-7} \) and \( 1.13 \times 10^{-8} \); A vs. C: \( P = 2.75 \times 10^{-5} \) and \( 1.36 \times 10^{-10} \); A vs. D: \( P = 1.46 \times 10^{-12} \) and \( 6.86 \times 10^{-15} \)).

The independent assessment by the physician using the VAS corresponded with the assessment by the patients and also confirmed the more rapid onset of the effect under treatment with the combination. Moreover, the differences of the combination compared with the other groups proved to be highly significant (Mann–Whitney test at time points 4 and 8 weeks: A vs. B: \( P = 1.96 \times 10^{-9} \) and \( 5.1 \times 10^{-13} \); A vs. C: \( P = 4.4 \times 10^{-7} \) and \( 3.4 \times 10^{-10} \); A vs. D: \( P = 3.1 \times 10^{-16} \) and \( 1.1 \times 10^{-21} \)).

The subgroup analysis in children aged 0–12 years confirmed this finding.

Safety of Application

In the course of the 8-week study, no adverse effect was detected. In one patient in the heparin group, a transient intensification of the itching was observed, which according to the investigators was likely connected with the underlying illness. The observation of local tolerance included the assessment of eczemas, blisters/urticaria, ulcers, excoration and folliculitis. No such case was reported. Accordingly, more than 88% of the patients assessed the local tolerability of the medication from Groups A–C as ‘good’ to ‘very good’. At both examination times, a statistically significant advantage for the combination group compared with the other groups was found (Mann–Whitney test at time points week 4 and week 8: A vs. B: \( P = 1.5 \times 10^{-9} \) and \( 8 \times 10^{-15} \); A vs. C: \( P = 1.5 \times 10^{-9} \) and \( 6 \times 10^{-5} \); A vs. D: \( P = 1.7 \times 10^{-9} \) and \( 2.3 \times 10^{-15} \)).

In the children aged 0–12 years, the local tolerability of the combination and of the cream base was evaluated as ‘good’ to ‘very good’ by 100% of the subgroup participants.

Discussion

In a previous double-blind trial with the same study medication, we had demonstrated significant superiority of the topical combination over the active-free inert control cream.\(^{10}\) The parameters tested in this previous study were erythema, itching and skin dryness, assessed on a four-step VRS. For the trial presented in this study, we chose the more adequate assessment of itching through a VAS and by SCORAD. The VAS approach provides a more reliable quantification of intergroup differences, and SCORAD, as a validated index, allows the comparison of the magnitude of effects with other trials.\(^{11}\) A recent 6-week trial found a reduction of SCORAD values by 19.8% with the application of a urea-containing moisturizer to patients with atopic dermatitis.\(^{12}\) Urea as a basic skin care treatment would be expected to give outcomes in the same range as the control cream used in our trial. In fact, the reduction of SCORAD values observed in our study was 21.5% from baseline in the control group after 8 weeks, compared with 70.5% in the combination group. The observed effects of the combination of levonemol and heparin as well as the effects of the single constituents, as assessed by SCORAD (Fig. 3), must therefore be considered clinically highly relevant.

Assessment of symptom improvement of atopic dermatitis by VAS has been applied by others, e.g. in a trial testing the effects of a topical combination of glycerylthetonic acid, telemesteine, grape extract, allantoin, levomelon, capryloyl glycine, hyaluronic acid, shea butter and tocopheryl acetate.\(^{2}\) The study reported an improvement by 23.9 mm within 6 weeks, whereas in our study the reduction of VAS score was 41.3 mm in 8 weeks and practically no change in the control group. Moreover, this comparison supports the conclusion of a high clinical relevance of our findings. Generally, differences of 6–10 mm on the VAS are regarded as clinically relevant,\(^{13–16}\) e.g. in pain assessment as a typical subjective parameter.

Whereas the difference between the combination and control treatments is clearly clinically relevant, the advantage of the combination treatment over the single treatment is less distinct, but still relevant. The differences of group A vs. B and A vs. C were 6–10 mm already after 4 weeks and 10–16 mm after 8 weeks. For both visits, it can be assumed that the patient will notice the advantage of the combination treatment not only over the control preparation but also over the single constituents.

The results of our study provide a rational and statistically comprehensible clinical justification for the combination treatment. At the same time, it provides evidence for the applicability in children of all age groups. The tendency towards a slightly (non-significantly) better efficacy in the subgroup of 7–12-year-old children could represent an artefact caused by the assessment made by the legal representatives for the 0–6-year-old participants.

Safety of application is an important pre-condition for skin care products regularly used by patients with atopic dermatitis. Rare cases of contact dermatitis have been reported with the use of bisabolol\(^{17,18}\) and heparin,\(^{19}\) although in the case of heparin cutaneous reactions seem to require sensitization through subcutaneous or intravenous exposure.\(^{20,21}\) The lack of intolerability reactions under application of the combination product in our study was therefore not overly surprising and speaks in favour of the safe and effective clinical use of the combination treatment from levomelon and heparin alone treatment, and in particular for use in children and young people. In this context, it is all the more significant that the preparation is applied to skin areas with an injured barrier function, which should lead to an increased probability of medication-induced intolerability reactions. This was proved not to be the case in this study.

Conclusion for clinical practice

This study confirms the anti-allergic, anti-inflammatory and healing mechanisms of action of levomelon and heparin as evident from clinical experience. The combination treatment is superior to the treatment with the two individual substances alone: the patients do not only profit from the additive effects of the two
individual substances but also from an earlier onset of a noticeable alleviation of itching – with simultaneous very good local tolerability.

References