2. Synopsis

Name of Company: bioskin GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Linolacort® Hydro 1.0 Creme Triamgalen® Creme (0.1 %) Betnesol®-V Creme (0.1 %) Elidel® 1 % Creme Basiscreme DAC		
Name of Active Ingredient: hydrocortisone, triamcinolone acetonide, betamethasone valevate pimecrolimus		

Title of Study:

A phase IV, single-center, randomized, controlled, observer-blind study to develop the atopic localized eczema regression test (ALERT) using marketed topical corticosteroid formulations of different strength and the calcineurin inhibitor pimecrolimus (Elidel®) in patients with a predisposition for atopic dermatitis

Investigator(s):

J. Fluhr, M.D.; H. Siemetzki, M.D.

Study center(s):

bioskin GmbH, Berlin, Germany

Publication (reference):

Not applicable to this trial

Studied period (years):	Phase of development:
2010	IV

Objectives:

To develop a regression test after repeated open washing with sodium lauryl sulfate (SLS) as a model for induced eczema in patients with a predisposition for atopic dermatitis

Methodology:

During the *screening phase* it was determined if the patients were eligible for the study by means of a single 24 h occluded epicutaneous test with 1 % SLS on the back. If the patients had a previous positive 24 h occluded epicutaneous test with 1 % SLS no re-exposure was required. Non-responders were not enrolled in the study. In the *induction phase* two test areas of approximately 10 x 5 cm each were identified on the volar forearms (one on each forearm) of each patient. Two comparable fields with localized eczema were induced in both test areas using the ROWT. The patients performed the washing. The length of the induction period (four to six days) depended on the individual response time of the patient three times per day. On visit Day 1 and Days 4 – 6 clinical assessments by scoring (erythema, scaling and fissures) as well as photodocumentation from both test areas were done and TEWL was measured. Mexametry was performed on Day 1. On Days 2 and 3 of the induction phase the patients came to bioskin and performed one of the three daily ROWT procedures at the site. In order to conclude the induction phase and enter the regression phase the average of the TEWL values on each volar forearm had to reach a mean value of 30 g/m^2 h with no more than 15 g/m^2 h difference between the lowest and the highest value of the three test fields per volar forearm. Only patients who met these criteria on both arms were randomized prior to the regression phase.
In six patients one biopsy was taken either from a test field treated with Betnesol®-V Creme or from an untreated test field at the end of the *regression phase.* Nine to 11 days later a follow-up visit for wound control was performed in these patients. A follow-up visit was also performed in case of clinically relevant side effects or strong ongoing eczematous reactions in the respective patient.

Number of subjects (planned and analyzed):

Fourteen male or female patients with a predisposition for atopic dermatitis were planned and enrolled in this study. The data from 13 of 14 enrolled patients were valid for the safety, ITT and PP analyses. One patient was excluded from all analyses since this patient failed to enter the regression phase.

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Diagnosis and main criteria for inclusion:

Men and women aged 18 to 55 years with medical disposition for atopic dermatitis according to Erlangen atopy score sum equal or higher than 10 points and no acute atopic dermatitis on the volar forearms and no clinically relevant eczema on the body but otherwise no history of other relevant dermatological or relevant systemic diseases; patients demonstrating irritative skin reaction to 24 h occluded epicutaneous test with 1 % SLS, i.e. 'responders'

Test product(s), dose and mode of administration, batch number:

Linolacort® Hydro 1.0 Creme (1.0 % hydrocortisone), batch no. 904070
Triamgalen® Creme (0.1 % triamcinolone acetonide), batch no. 09352
Betnesol®-V Creme (0.1 % betamethasone valerate) batch no. C414859
Elidel® 1 % Creme (1.0 % pimecrolimus), batch no. W0673
Basiscreme DAC, batch no. 290404BS-3

Topical semi-occlusive application of approx. 200 µl cream per test field (4.9 cm^2) on the volar forearm once daily

Duration of treatment:

4-day treatment period (three treatments)

Reference therapy or controls, dose and mode of administration, batch number:

n.a.

Duration of treatment:

n.a.

Criteria for evaluation:

Efficacy:

- TEWL measurements (Day 1 in induction phase, Days R1, R2, R3 and R4 in regression phase)
- AUC of TEWL measurements in regression phase
- Change from end-of-induction phase in TEWL (R2 – R1, R3 – R1, R4 – R1)
- Change from baseline in TEWL (R1 – Day 1, R2 – Day 1, R3 – Day 1, R4 – Day 1)
- Mexametry measurements (Day 1 in induction phase, R1, R2, R3 and R4 in regression phase)
- Change from end-of-induction phase in mexametry (R2 – R1, R3 – R1, R4 – R1)
- Change from baseline in mexametry (R1 – Day 1, R2 – Day 1, R3 – Day 1, R4 – Day 1)
- Clinical assessment of erythema, scaling and fissures (all visits)

Additionally, histology assessments of skin biopsies taken on Day R4 in six patients

Safety: Screening and final clinical examination, recording of adverse events

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Statistical Methods:

Study populations

The Full Analysis Set (FAS) included all randomized patients who successfully completed the induction phase and entered the regression phase, who had at least one dose of study medication and had valid TEWL measurements on Days R1 and R4. The ITT analysis is based on the FAS.

The Valid-Cases Set included all patients in the FAS, excluding patients with major protocol violations or significant protocol deviations.

Major protocol violations included but were not limited to:

- inappropriate enrollment
- the use of prohibited concomitant medication
- application of topical formulations other than the study preparations in the test field area
- reaching a major exclusion criterion during the trial

Significant protocol deviations included:

- identified protocol violations or significant deviations during the internal “Patient Data Inclusion” meeting (Principle investigator and statistician)

The PP analysis is based on the Valid-Cases Set.

Statistical methods

The study was descriptively evaluated. No formal hypotheses were formulated in this exploratory study. Any calculation of confidence intervals or p-values are descriptively interpreted.

Descriptive statistics (valid n, mean, standard deviation, median, minimum and maximum) were used to summarize the absolute outcomes for TEWL and mexametry measurements as well as change from the end-of-induction phase and change from baseline by treatment and study day. The AUC of TEWL assessments in the regression phase is presented accordingly by treatment. The measurements of the induction phase are presented by the destined treatment of the fields as well as pooled over all test fields.

Treatment effects expressed as pair-wise differences in AUC, TEWL and change from end-of-induction phase in TEWL, respectively, were evaluated by two-sided confidence intervals with coverage probability of 95 % of the mean difference.

The clinical assessments of erythema, scaling and fissures are presented by frequency tables by treatment and visit. The total clinical assessment score was determined as the sum of the individual clinical assessments of erythema, scaling and fissures for each patient, treatment and visit and is presented applying descriptive statistics.

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Summary, conclusions:

Efficacy results:

A precondition for developing an Atopic Localized Eczema Regression Test (ALERT) is the homogeneity of induced eczema in test areas in patients with a predisposition for atopic dermatitis. Following standardized washing with 2 % SLS over maximal six days, sufficient experimentally induced localized eczema in a comparable manner was reached when evaluating TEWL and erythema measured by mexametry as well as the clinical assessment scores.

The following 4-day regression phase with three topical applications under semi-occlusive conditions with three corticosteroid formulations of different strength (Betnesol®-V Creme, Triamgalen® Creme and Linolacort® Hydro 1.0 Creme), the calcineurin inhibitor pimecrolimus (Elidel®) and Basiscreme DAC showed that the healing process was very fast under all treatments, even in the untreated test field. This was reflected by a clear decrease in mean TEWL and mean mexametry values already on Day R2. However, the extent of reduction in mean TEWL and mean erythema differed as follows:

The greatest decrease in mean TEWL on Day R2 was noted for Betnesol®-V Creme (mean change R2-R1: -23.98 g/m²h), followed by Basiscreme DAC (-17.92 g/m²h). The next greater reduction was noted for the untreated control (-15.02 g/m²h). A lesser decrease was seen for Triamgalen® Creme and Linolacort® Hydro 1.0 Creme (-13.58 and -13.13 g/m²h, respectively). The lowest decrease was noted for Elidel® 1 % Creme (-7.82 g/m²h).

On Day R3 and R4 the mean TEWL values had further decreased in all test fields. But a positive effect compared to untreated control, reflected by a greater reduction in TEWL was only seen for Betnesol®-V Creme at end of the regression phase (Day R4). Only 4-day treatment with Betnesol®-V Creme revealed a mean TEWL which had returned to a value of normal skin (mean TEWL: 9.28 g/m²h). Lowest decreases at end of study were seen for Triamgalen® Creme and Elidel® 1 % Creme with mean TEWL values of 17.35 and 17.41 g/m²h, respectively. The mean TEWL values for Linolacort® Hydro 1.0 Creme, Basiscreme DAC and the untreated control were 14.27, 12.44 and 12.56 g/m²h, respectively on Day R4.

In the treatment comparisons of AUC of TEWL measurements at regression phase a statistically significant greater decrease was seen for Betnesol®-V Creme (mean AUC: 55.88 a.u), when compared to Linolacort® Hydro 1.0 Creme, Triamgalen® Creme, Elidel® 1 % Creme and to untreated control (73.10, 80.38, 81.23 and 71.45 a.u., respectively). No statistically significant difference was found between Betnesol®-V Creme and Basiscreme DAC (62.98 a.u.)

Statistically significant greater decreases were also found for Basiscreme DAC when compared to Linolacort® Hydro 1.0 Creme, Triamgalen® Creme, Elidel® 1 % Creme and to untreated control. Also the untreated control showed statistically significant greater decreases when compared to Triamgalen® Creme and Elidel® 1 % Creme. Furthermore, a statistically significant greater decrease was found for Linolacort® Hydro 1.0 Creme when compared to Elidel® 1 % Creme.

No statistically significant differences were found between Triamgalen® and Linolacort® Hydro 1.0 Creme, between Triamgalen® and Elidel® 1 % Creme as well as between untreated control and Linolacort® Hydro Creme 1.0.

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Summary, conclusions:

<u>Efficacy results (continued):</u>

The results of the mexametry measurements showed a similar decrease in erythema for Betnesol®-V Creme, Basiscreme DAC and the untreated control (mean change R2-R1: -71.85, -63.85 and -79.56 a.u., respectively). Lesser reductions of erythema were noted for Linolacort® Hydro 1.0 Creme and Elidel® 1 % Creme (-62.43 and -48.90 a.u., respectively). The lowest decrease in mean mexametry values was noted for Triamgalen® Creme (-29.28 a.u.).

At the following assessment points (Day R3 and R4) the mean mexametry values remained nearly constant in the test fields treated with Basiscreme DAC and in the untreated test field. In the test field treated with Betnesol®-V Creme a further reduction of erythema was noted on Day 4 (-91.44 a.u.), representing the greatest decrease of erythema among all treatments over the study period. In the test fields treated with Linolacort® Hydro 1.0 Creme and Triamgalen® Creme the mean mexametry values had increased on Day R3. On Day R4 the mean mexametry value remained constant for Linolacort® Hydro 1.0 Creme and decreased again for Triamgalen® Creme (-43.69 and -42.28 a.u., respectively). The mean mexametry value had also slightly increased in the test fields treated with Elidel® 1 % Creme on Day 3 which then decreased again on Day 4 (-57.54 a.u).

In general the results of the total clinical assessment reflect the data of the clinical assessment of erythema since scaling and fissures occurred only in single cases. A reduction of erythema was seen in all test fields during the regression phase. The median had decreased from 2 to 1.

A somewhat faster reduction of erythema was observed following treatment with Linolacort® Hydro 1.0 Creme and Basiscreme DAC (median = 1 on Day R2), followed by Betnesol®-V Creme, Elidel® Creme and the untreated control (median = 1 on Day R3) and at last Triamgalen® Creme (median = 1 on Day R4).

Overall, a plausible differentiation of preparations was not possible under the conditions in this model. The healing process was very fast under all treatments, even in the untreated field. A positive effect compared to untreated control was only seen for Betnesol®-V Creme. Furthermore, the expected differentiation regarding treatment response of the three different corticosteroid classes could not be reproduced.

In the histology assessment of skin biopsies taken on Day R4 a relevant difference was only seen for the dendritic cell marker CD1a: a clearly lower quantity of CD1a was noted for the samples treated with Betnesol®-V Creme compared to untreated control.

No relevant differences in the proportion were observed for any of the other inflammatory cell markers (CD4, CD8, CD20, CD68, Ki-67 and neu Ela), the percentage of filaggrin as well as in the epidermal thickness between the area treated with Betnesol®-V Creme und the untreated control.

<u>Safety results:</u>

There were no adverse events reported in this study and the final physical examination did not show relevant findings in any of the subjects. Therefore, there were no safety concerns to this study.

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Summary, conclusions (continued):

Conclusion:

The purpose of this study was to develop a regression test after repeated open washing with SLS as a model for induced eczema in patients with a predisposition for atopic dermatitis using marketed topical corticosteroid formulations of different strength as well as the calcineurin inhibitor pimecrolimus (Elidel®).

The present Atopic Localized Eczema Regression Test (ALERT) with a 4-day regression phase (three treatments) did not show the expected differentiation of treatments which was confirmed by TEWL and mexametry measurements as well as clinical assessment.

Despite of the fact that all of the used active formulations (three corticosteroid formulations of different strength [Betnesol®-V Creme, Triamgalen® Creme and Linolacort® Hydro 1.0 Creme], the calcineurin inhibitor pimecrolimus [Elidel®]) are well accepted therapies for atopic dermatitis, apparently the target mechanism of these could not be reflected in this model. The ALERT model in the current form does not provide plausible results.

The following observations challenge the suitability of the regression part of this model:

The healing process was very fast under all treatments, even in the untreated field .

A positive effect compared to untreated control was only seen for Betnesol®-V Creme, reflected by a greater reduction in TEWL.

Furthermore, Basiscreme DAC showed a better reduction in TEWL when compared to the other two steroids as well as compared to Elidel®. A slight delay in healing following treatment with Linolacort® Hydro Creme, 1.0 Triamgalen® Creme and Elidel® 1 % Creme might be a possible explanation.

In the histology assessment of skin biopsies taken on Day R4 a relevant difference was only seen for the dendritic cell marker CD1a: a clearly lower quantity of CD1a was noted for the samples treated with Betnesol®-V Creme compared to untreated control.

No relevant differences in the proportion were observed for any of the other inflammatory cell markers (CD4, CD8, CD20, CD68, Ki-67 and neu Ela), the percentage of filaggrin as well as in the epidermal thickness between the area treated with Betnesol®-V Creme und the untreated control.

Even though in one of the early studies the histological and immunohistochemical results showed strong similarities between the induced eczema in this model and atopic dermatitis lesions, it seems that the chronic character of the disease could not be exactly mimicked in the present model.

There were no adverse events and no other observations related to safety in this study.

Date of the report: June 07, 2010