Clinical Study Report

Sponsor:	**Almirall Hermal GmbH**
Trial No.:	**H 527 000-0917 / 290709BS**
EudraCT-No.:	2009-017407-28
Title:	A phase II, single-center, randomized, controlled, double-blind study to assess effects on skin conditions and patient reported outcome of a topical formulation containing LAS41002 on lesional skin in patients with atopic eczema
Investigational Product/s:	Mometasone cream (0.1 % mometasone furoate) Ecural® Fettcreme (0.1 % mometasone furoate)
Clinical Phase:	II
Objective:	To evaluate the effects on clinical skin conditions and the satisfaction of patients of two different topical mometasone formulations in patients with mild to moderate atopic eczema
Description:	This phase II, single-center, randomized, controlled trial was double-blind with intraindividual comparison of the treatments to the test fields. Altogether 20 male or female patients, aged 18 years or older with mild to moderate atopic dermatitis and at least two comparable lesional areas were included in the trial to evaluate the effects on clinical skin conditions and the patients' satisfaction with two different topical mometasone formulations. There were no dropouts. Data from all 20 patients were valid for the safety, intent-to-treat (ITT) and per-protocol (PP) analyses. All 20 patients received all treatments with random assignment to the test fields. Altogether two comparable treatment areas (difference in local scoring atopic dermatitis [SCORAD] not greater than 3) on opposite extremities of 100 - 300 cm^2 were examined per patient. Each treatment area was treated with approximately 200 - 600 µl of each investigational product once daily by the patients at home during a 2-week treatment period. Skin conditions were determined by scoring (erythema, edema/papulation, oozing/crusts, excoriations, lichenification, dryness, itching) and determination of stratum corneum hydration by corneometry on Days 1 (baseline), 8 and 15. On Day 1 and at the end of treatment questionnaires were filled out by the patients.
Principal Investigator:	[redacted] bioskin GmbH Burchardstrasse 5, 20095 Hamburg, Germany [redacted] [redacted]
Clinical Trial Manager (Sponsor):	[redacted] Almirall Hermal GmbH Scholtzstrasse 3 21465 Reinbek, Germany [redacted] [redacted]
GCP Compliance:	The clinical trial was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Trial Period:	February 10 to March 29, 2010
Date of Report:	July 14, 2010

2. Synopsis

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Not applicable (n.a.)	Volume: Page:	
Name of Active Ingredient: Mometasone furoate		

Title of Study:
A phase II, single-center, randomized, controlled, double-blind study to assess effects on skin conditions and patient reported outcome of a topical formulation containing LAS41002 on lesional skin in patients with atopic eczema

Investigator(s):
[redacted]

Study center(s):
bioskin GmbH, Hamburg, Germany

Publication (reference):
Not applicable to this trial

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

Objectives:
To evaluate the effects on clinical skin conditions and the satisfaction of patients of two different topical mometasone formulations in patients with mild to moderate atopic eczema

Methodology:
Altogether two comparable treatment areas (difference in local SCORAD not greater than 3) of 100 - 300 cm^2 on opposite extremities were examined per patient. The treatment area was defined as the entire ventral forearm in case of lesions on the arms or as the entire ventral lower leg in case of lesions on the leg. At least one lesional region within each of these areas had to cover ≥ 20 cm^2. Approximately 2 mg/cm^2 of the investigational products (same amount for each treatment area) were applied to the respective treatment area once daily by the patients at home over a 2-week treatment period. On Days 8 and 15 the application must not have been performed before the visit to bioskin. Skin conditions were determined by scoring (erythema, edema/papulation, oozing/crusts, excoriations, lichenification, dryness, itching) and determination of stratum corneum hydration by corneometry on Days 1 (baseline), 8 and 15. On Day 1 and at the end of treatment questionnaires were filled out by the patients.

Number of subjects (planned and analyzed):
Twenty male or female patients were planned and included in the trial. There were no dropouts. Data from all 20 patients were valid for the safety, ITT and PP analyses.

Diagnosis and main criteria for inclusion:
Male or female patients, aged 18 years or older with mild to moderate atopic dermatitis and at least two comparable lesional areas

Test product(s), dose and mode of administration, batch number:
Mometasone cream (0.1 % mometasone furoate), batch no. K0527/20
Topical application of approximately 200 - 600 µl cream per test area (100 - 300 cm^2)

Duration of treatment:
Once daily over a 14-day treatment period

Reference therapy or controls, dose and mode of administration, batch number:
Ecural® Fettcreme (0.1 % mometasone furoate), batch no. K0190/4720
Topical application of approximately 200 - 600 µl cream per test area (100 - 300 cm^2)

Duration of treatment:
Once daily over a 14-day treatment period

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: n.a.		
Name of Active Ingredient: Mometasone furoate		

Criteria for evaluation:

Efficacy:

- Clinical assessment (local SCORAD intensity criteria: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, dryness, itching) by scoring
- Measurement of stratum corneum hydration by corneometry
- Skin penetration time after first application
- Questionnaire regarding cosmetic traits and the patients' satisfaction with the product
- Questionnaire regarding the live quality (DLQI)

Safety: Medical history and physical examination including vitals signs (blood pressure and pulse rate) were assessed at screening. A final physical examination was performed on the last study day. Recording of adverse events.

Statistical Methods:

Analysis populations

Efficacy populations

Intent-to-treat (ITT): The full analysis set included all randomized patients who received at least one dose of study medication, and had at least one post-baseline assessment. The ITT analysis was based on the full analysis set.

Per-protocol (PP): The valid-cases set included all patients

- without any major protocol violation including violation of inclusion criteria;
- who received the full trial medication doses, except for treatment discontinuation due to treatment related adverse events or lack of efficacy;
- with available values of the efficacy variables at all days, i.e. with no imputed values, except for treatment discontinuation due to treatment related adverse events or lack of efficacy.

Prior to breaking the blind, other additional criteria might have been added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that result in noteworthy study protocol violations.

The per-protocol analysis was based on the valid-cases set.

Safety population

The safety population was comprised of all patients who received any study medication at least once. All safety analyses were based on the safety population.

Hypotheses

No formal hypotheses were postulated. All analyses are explorative and are interpreted non-confirmatory. Descriptive statistics were used in order to evaluate trends and establish the differences in effect of the treatments.

Statistical analyses

Standard descriptive statistics as valid n, mean, standard deviation, median, minimum and maximum are presented for cardinally scaled data. An inter-quartile range and a 95 % confidence interval of the mean were provided where appropriate. Categorical data and assessment scores are presented by frequency tables. An ITT and PP analysis are provided for efficacy parameters (local SCORAD and corneometry). The analysis of cosmetic traits and DLQI was limited to the PP population.

(continued)

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: n.a.	Volume: Page:	
Name of Active Ingredient: Mometasone furoate		

Statistical Methods (continued):

Analysis of efficacy data

The total clinical assessment score was determined as the sum of the individual clinical assessments of erythema, edema/papulation, oozing/crusts, excoriations, lichenification, dryness and itching (local SCORAD intensity scale) for each patient, treatment and visit and is presented by treatment and visit providing descriptive statistics. Changes from baseline in total clinical assessment score and their differences between the two treatments are presented accordingly, together with 95 % confidence intervals of the means. Individual scores are presented by treatment and visit providing frequency tables and standard descriptive statistics. The assessment of stratum corneum hydration by corneometry was evaluated descriptively by treatment and visit, providing descriptive statistics for the absolute values, for the changes from baseline and for differences in change from baseline between the two treatments. In addition to the standard descriptive statistics the 95 % confidence intervals of the mean are provided.

Analysis of cosmetic traits

The outcomes of the questionnaire regarding cosmetic traits and the patients' satisfaction with the product are presented providing frequency tables by treatment, where appropriate. Comparisons between treatments were performed applying the sign test, as distribution free and robust procedure. The assessment of the first visible effect is presented by frequency tables. The incidence of any visible effect is presented by frequency tables and the time point of first visible effect is presented by descriptive statistics. Skin penetration is presented by frequency tables for each time point and treatment. If the first question was answered with "YES" for both treatment areas earlier than 60 minutes the remaining time points were disregarded during the conduction of the trial, but were replaced by "YES" for the analysis. A derived variable skin penetration progress is provided, which was defined as a composite outcome of the two questions as

- "sufficiently soaked in" if the first question was answered with "Yes",
- "accelerated progress", if the first question was answered with "No" and the respective test area "felt more ready" according to the second question, and
- "not sufficiently soaked in" otherwise.

Additionally, the time point of sufficient soak in is presented as 15, 30, 45 and 60 minutes after application or "not sufficiently soaked in".

Analysis of quality of life

Outcomes of the 10 questions of the DLQI questionnaire surveyed on Day 1 (baseline) and Day 15 (end of study) are presented by frequency tables. For each visit the DLQI was determined as the sum of the 10 scores. Additionally derived item-specific scores were determined as the sum of specific scores under the following headings:

- Symptoms and feelings: questions 1 and 2
- Daily activities: questions 3 and 4
- Leisure: questions 5 and 6
- Work and School: question 7
- Personal relationships: questions 8 and 9
- Treatment: question 10

Descriptive statistics are provided for the DLQI and the derived item-specific scores for both visits, as well as for their changes from baseline.

Safety analyses

Safety was evaluated by tabulations of extent of exposure to study drug, adverse events (AEs) and vital signs.

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: n.a.		
Name of Active Ingredient: Mometasone furoate		

Summary, conclusions:

Efficacy results:

Under the present study conditions with once daily application of Mometasone cream (0.1 % Mometasone furoate) over a 2-week treatment period a clear positive effect on clinical skin conditions and patients' satisfaction was seen.

The test fields to be treated with Mometasone cream and Ecural® Fettcreme were comparable at baseline regarding

- size of the mean treatment areas (175.5 and 175.3 cm^2),
- severity of the lesions evaluated by clinical assessment (SCORAD intensity criteria) showing generally moderate erythema, edema/papulation, lichenification, dryness and itching (median = 2, each), mild excoriations (median = 1) and oozing/crusts only in a few patients (median = 0) and total sign score (TSS) (median = 10.5 and 11, respectively),
- skin hydration assessed by corneometry (12.9 and 13.1 a.u.),
- itching assessed by first question of the questionnaire concerning "the cosmetic traits and patients' satisfaction with the product" showing moderate itching in 60 % of the patients.

Occurrence and intensity of erythema, edema/population, dryness, itching as well as the TSS had clearly decreased over the study period following treatment with Mometasone cream and Ecural® Fettcreme.

A slightly greater improvement in erythema was seen in the test fields treated with Ecural® Fettcreme when compared to Mometasone cream (Day 15: median = 0.0 and 0.5, respectively). No erythema was noted in more patients in the test fields treated with Ecural® Fettcreme (65.0 %) than in the test fields treated with Mometasone cream (50.0 %) at end of the study.

The reduction in edema/papulation was comparable for both treatments (Day 15: median = 0.0, each). Edema/papulation was absent in 80 % of patients in the test fields treated with Mometasone cream and in 75.0 % of patients in the test fields treated with Ecural® Fettcreme at end of treatment.

No oozing/crusts and no excoriations were observed in any patient either in the test fields treated with Mometasone cream or in those treated with Ecural® Fettcreme at end of the study (Day 15: median = 0.0, each).

The occurrence and intensity of lichenification slightly changed over the study period following treatment with Mometasone cream and Ecural® Fettcreme (Day 15: median = 1, each). At end of the treatment phase (Day 15) mild lichenification was seen in more than half of the patients (55.0 %) following both treatments.

A comparable decrease was seen for dryness following treatment with Mometasone cream and Ecural® Fettcreme (Day 15: median = 0.0, each). Dryness was absent in more than half of the patients in the test fields treated with Mometasone cream (65.0 %) and Ecural® Fettcreme (60.0 %) at end of the study.

A comparable reduction was also noted for itching following treatment with Mometasone cream and Ecural® Fettcreme (Day 15: median = 0.0, each). Itching was absent in the majority of patients (90.0 % and 95.0 %, respectively) at end of the study.

At the end of the study the TSS had comparably decreased for Mometasone cream and Ecural® Fettcreme (Day 15: median = 0.0, each). The median change from baseline in TSS was -8.5 for Mometasone cream and -8.0 for Ecural® Fettcreme. The statistical comparisons between Mometasone cream and Ecural® Fettcreme showed no significant differences in mean change from baseline of the TSS at any test point.

(continued)

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: n.a.		
Name of Active Ingredient: Mometasone furoate		

Summary, conclusions:

Efficacy results (continued):

The corneometry measurements showed that treatment of atopic eczema lesions with Mometasone cream and Ecural® Fettcreme led to a comparable increase in skin hydration over the 2-week treatment period (Day 15: 25.8 and 24.0 a.u., mean change to baseline: 12.9 and 10.9 a.u., respectively). The statistical comparisons between Mometasone cream and Ecural® Fettcreme showed no significant differences in mean corneometric values compared to baseline at any test point.

The following statements of the questionnaire regarding cosmetic traits and the patients' satisfaction were rated clearly better for Mometasone cream than for Ecural® Fettcreme:

- "The application of the cream is easy and convenient" (completely applicable: 90.0 % and 65.0 %, respectively),
- "The cream is convenient for daily application" (completely applicable: 70.0 % and 40 %, respectively),
- "The cream permeates quickly" (completely applicable: 50.0 % and 10.0 %, respectively)
- "The cream is well distributable" (completely applicable: 60.0 % and 20.0 %, respectively),
- "I prefer cream" (yes: Mometasone cream: 75.0 %, Ecural® Fettcreme: 25.0 %).

The following statement of the this questionnaire was assessed somewhat better for Ecural® Fettcreme than for Mometasone cream:

- "The cream is suitable for the application on inflamed and sensitive skin" (completely applicable: 70.0 % and 60.0 %, respectively).

The following statements of the questionnaire were assessed as comparable for Mometasone cream and Ecural® Fettcreme:

- "I like the application of this cream more than the treatment I used before" (completely or extensively applicable: 55.0 % and 50.0 %, respectively),
- "Visible effect" (yes: 100.0 %, each),
- "The first effect was visible" (approximately after two days, both),
- "How has your skin condition improved?"(completely or visible: 100.0 %, each),
- "How do you assess the tolerability of the creams?"(very good or good: 100.0 %, each),
- "How do you assess the itching of your skin after repeated application?"(no itching 60.0 %, each),
- "I would recommend the cream for other patients" (yes: 95.0 %, each).

The statistical comparisons between Mometasone cream and Ecural® Fettcreme showed significant differences regarding the following statements: "The cream is convenient for daily application" ($p = 0.0391$), "The cream permeates quickly" ($p = 0.0063$) and regarding the preference of the cream ($p = 0.0414$) in favor of Mometasone cream. No statistically significant differences were noted for the remaining statements and questions.

The skin penetration progress was assessed as sufficiently soaked in in all 20 patients for both study preparations at the latest 60 minutes after application. The statistical comparisons between Mometasone cream and Ecural® Fettcreme showed no significant differences in skin penetration at any time point (15 minutes, 30 minutes, 45 minutes, 60 minutes).

(continued)

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: n.a.	Volume: Page:	
Name of Active Ingredient: Mometasone furoate		

Summary, conclusions:

Efficacy results (continued):

The median DLQI summing the score of six headings (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment) had decreased from a moderate effect on patient's life (Day1: 7.0) to a small effect on patient's life (Day 15: 2.0) (median change to baseline: -3.5).

The questionnaire results about the quality of life showed a clear improvement concerning symptoms and feelings of the patients over the course of the study (median change from baseline: -2.0). Symptoms like itchy, sore, painful or stinging were absent in half of the patients (50.0 %) or were assessed as little in most of the remaining patients. In more than half of the patients (65.0 %) no embarrassment or self-consciousness because of skin was noted. A clear improvement was also noted regarding the daily activities. More than half of the patients (65.0 %) reported no interference with going shopping or looking after home or garden by their skin. No influence of skin on the choice of clothes was noted in the majority of patients (70.0 %). During the study period a slight improvement was seen concerning the leisure and social activities. The majority of patients (80.0 %) found that their skin did not affect any social or leisure activities. More than half of the patients (65.0%) reported no difficulties to do sport. A slight improvement was also observed regarding the work and school over the course of the study. All 20 patients reported that the skin did not prevent them from working or studying and most of the patients (75.0 %) found that the skin had not been a problem at work or studying. No relevant changes were noted concerning the personal relationships over the course of the study. The majority of patients (85.0 %) reported no problems with their partner or any of their close friends/relatives due to their skin and most of the patients (70.0 %) noted no sexual difficulties caused by their skin. Most of the patients (75.0 %) noted no problem with the treatment of their skin.

Safety results:

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

2. Synopsis (continued)

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: n.a.	Volume: Page:	
Name of Active Ingredient: Mometasone furoate		

Summary, conclusions:

Conclusion:

The aim of the study was to investigate the effects on skin conditions and patient reported outcome of a topical formulation containing mometasone (LAS41002) on lesional skin in patients with atopic eczema.

Under the conditions in this study a clear positive effect on skin properties and patients' satisfaction was observed over a 2-week treatment period. This was confirmed by a clinically relevant improvement in clinical assessment scores, an increase in skin hydration as well as by the questionnaires concerning cosmetic traits, patients' satisfaction, skin penetration and quality of life.

The effect was generally comparable to Ecural® Fettcreme regarding clinical assessment and corneometry:

Erythema, edema/population, dryness, itching as well as the TSS had clearly decreased over the study period following treatment with Mometasone cream and Ecural® Fettcreme, whereas Ecural® Fettcreme showed a slightly greater improvement of erythema. No oozing/crusts and no excoriations were observed in any patient either in the test fields treated with Mometasone cream or in those treated with Ecural® Fettcreme at end of the study. Lichenification slightly changed over the study period following treatment with Mometasone cream and Ecural® Fettcreme. The statistical comparisons between both mometasone formulations showed no significant differences in mean change from baseline of the TSS.

The corneometry measurements showed that treatment of atopic eczema lesions with Mometasone cream and Ecural® Fettcreme led to a comparable increase in skin hydration. The statistical comparisons between both formulations showed no significant differences in mean corneometric values compared to baseline.

The results of the questionnaire regarding cosmetic traits and the patients' satisfaction showed a clearly better rating for Mometasone cream than for Ecural® Fettcreme with respect to convenient and daily application, permeation and distribution and most of the patients would prefer Mometasone cream. The suitability for the application on inflamed and sensitive skin was assessed as somewhat better for Ecural® Fettcreme. Approximately half of the patients liked the application of the two present formulations more than the treatment they used before.

All patients reported a visible effect and a complete or visible improvement following treatment with both formulations and the tolerability of both creams was assessed as very good or good. No itching was present in more than half of the patients after repeated application of both creams. Nearly all patients would recommend both creams for other patients.

The DLQI summing the score of six headings (symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment) had decreased from a moderate to a small effect on the patient's life.

Date of the report: July 14, 2010