Clinical Study Report

Sponsor:	**Almirall Hermal GmbH**
Study no.:	**H 527000 - 0805 / 280307BS**
EudraCT-no.:	**2008-002141-24**
Title:	A phase II, single-center, randomized, controlled, observer-blind study to determine the non-inferiority of a topical mometasone formulation vs a marketed comparator by evaluation of the anti-psoriatic efficacy in a psoriasis plaque test
Study preparation:	Mometasone cream (0.1 % mometasone furoate) Active ingredient-free vehicle to Mometasone cream **Comparator:** Ecural® Fettcreme (0.1 % mometasone furoate)
Clinical phase:	II
Indication:	Psoriasis
Description:	Twenty-two male or female subjects with stable psoriatic plaques were randomized in this randomized, controlled, observer-blind study. There were no dropouts. The data of all 22 subjects were valid for the intention-to-treat (ITT) and per-protocol (PP) analyses. Treatments were randomly assigned to the test fields. Altogether three test fields were examined per subject. The test fields on psoriatic skin were descaled and treated occlusively (Mometasone cream, 0.1 %, active ingredient-free vehicle to Mometasone cream and Ecural® Fettcreme) over a study period of 12 days (10 treatments). Sonography and chromametry were made at baseline (day 1) and on study days 4, 8 and 12, clinical assessments were made on study days 4, 8 and 12, photo documentation was made on study days 1 and 12.
Principal Investigator:	[redacted] bioskin GmbH Bergmannstrasse 5, 10961 Berlin, Germany [redacted]
Clinical Trial Manager:	[redacted] Almirall Hermal GmbH Scholtzstr. 3, 21465 Reinbek, Germany [redacted]
GCP Compliance:	The study was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Study dates:	June 23 to July 25, 2008
Date of Report:	February 05, 2009

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: n.a.	Volume: Page:	
Name of Active Ingredient: 0.1 % mometasone furoate		

Title of Study: A phase II, single-center, randomized, controlled, observer-blind study to determine the non-inferiority of a topical mometasone formulation vs a marketed comparator by evaluation of the anti-psoriatic efficacy in a psoriasis plaque test	
Investigator(s): [redacted]	
Study center(s): bioskin GmbH, Berlin, Germany	
Publication (reference): Not applicable to this study	
Studied period (years): 2008	Phase of development: II
Objectives: To determine the non-inferiority of a new topical corticosteroid formulation vs a marketed product in a psoriasis plaque test	
Methodology: Ten occlusive treatments with study preparations and comparator (Ecural® Fettcreme) over a 12-day study period. Sonography was made at baseline (day 1) and on days 8 and 12, clinical assessments on days 8 and 12 and photodocumentation at baseline and on day 12.	
Number of subjects (planned and analyzed): Twenty-two male or female subjects planned and enrolled, there were no dropouts, data of all 22 subjects were valid for the ITT and PP analyses.	
Diagnosis and main criteria for inclusion: Male or female subjects with chronic plaque type psoriasis, aged 18 or older	
Test product(s), dose and mode of administration, batch number: Mometasone cream (0.1 % mometasone furoate), batch no. K0527/3 Active ingredient-free vehicle to Mometasone cream (01 %), batch no. K0527/4	
Duration of treatment: 12-day study period (10 treatments)	
Reference therapy or controls, dose and mode of administration, batch number: Ecural® Fettcreme (0.1 % mometasone furoate), batch no. K0190/72	
Duration of treatment: 12-day study period (10 treatments)	

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: 0.1 % mometasone furoate		

Criteria for evaluation:

Efficacy: Primary efficacy variable for statistical evaluation was the area under the time curve (AUC) calculated from infiltrate thickness differences to baseline calculated for the three measurement points following the baseline visit, separately.

Secondary variables were the infiltrate thickness (sonography), and the clinical assessment (scores) assessed or measured at the various test points.

Safety: Screening and final clinical examinations, recording of adverse events.

Statistical Methods:

Analysis populations

Efficacy populations

The Full Analysis Set consisted of all subjects randomized into the study who received at least one application of the study drug. To be included in the analysis, data from at least one postbaseline measurement had to be available. The Last Observation Carried Forward (LOCF) method was applied for missing efficacy measurements and assessments. The intention-to-treat (ITT) analysis was based on the Full Analysis Set.

The Valid-Cases Set included all subjects in the Full-Analysis Set, excluding subjects 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
- reaching a major exclusion criterion during the trial

Significant protocol deviations included:

- missing visits on days 4, 8, 12
- identified protocol violations or significant deviations during the “Subject Data Inclusion” meeting

The per-protocol (PP) analysis was based on the Valid-Cases Set.

Safety population

The Safety Set included all randomized subjects who received at least one application of study medication. All safety analyses were based on the Safety Set.

Analysis variables

Subject characteristics:

- Demographic and background characteristics
- Prior and concomitant medications

Efficacy part:

- Sonographic measurements (infiltrate thickness)
- Change to baseline in infiltrate thickness
- AUC of the changes in infiltrate thickness
- Global clinical assessment

Safety data:

- Adverse events
- Physical examination
- Vital signs

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: 0.1 % mometasone furoate		

Statistical Methods (continued):

Statistical Methods

Analysis of demographic data

Demographic and background data were summarized using descriptive statistical methods. Continuous data were summarized by mean, standard deviation, median and range. Categorical demographic data were summarized by frequency tables. Previous and concomitant medications were listed.

Discontinuations and dropouts

Subjects discontinuing the study were listed in the clinical study report with reason for discontinuation and last study day given.

Analysis of efficacy data

Calculation of the change in infiltrate thickness:

Differences to baseline were calculated for study days 4, 8 and 12 as

$dINF_X = INF_X - INF_1$ where x = (4, 8, 12).

Calculation of the AUC of the infiltrate thickness:

The AUC of the infiltrate thickness difference was calculated using the trapezoid rule, which reduced in this case to

$AUC(dINF) = ½ \bullet (7 \bullet dINF_4 + 8 \bullet dINF_8 + 4 \bullet dINF_{12})$

Hypotheses

Primary endpoint for this study was the non-inferiority of Mometasone cream (0.1 % mometasone furoate) to Ecural® Fettcreme using a non-inferiority margin $\Delta = 250$ with respect to the AUC of the change to baseline in infiltrate thickness, with a lower AUC being superior.

The following null-hypothesis H_{01} was tested versus the alternative H_{11}:

$H_{01}: \mu_T - \mu_S > 250$ and $H_{11}: \mu_T - \mu_S \leq 250$

with μ_T and μ_S as mean AUC of changes in infiltrate thickness for the test product Mometasone cream (0.1 % mometasone furoate) and the standard product Ecural® Fettcreme.

A secondary endpoint was the superiority of Mometasone cream (0.1 % mometasone furoate) to the active ingredient-free vehicle to Mometasone cream with respect to the AUC of change to baseline in infiltrate thickness.

The following null-hypothesis H_{02} was tested versus the alternative H_{12}:

$H_{02}: \mu_T - \mu_V > 0$ and $H_{12}: \mu_T - \mu_V \leq 0$

with μ_T and μ_V as mean AUC of changes in infiltrate thickness for the test product Mometasone cream (0.1 % mometasone furoate) and the vehicle.

An interim analysis was not planned.

During the statistical analysis according to the SAP (Version 1.0 from August 7, 2008) it was noted that the differences in infiltrate thickness at baseline (TP1) in one subject were clearly higher compared to all other subjects. After a reevaluation by another internal experienced evaluator there were discrepancies between the original and the reevaluation indicating a mistake in the first evaluation. Thus the sponsor decided to reevaluate all sonography images by an external independent specialist (Dr. J.-J. Levy, Berlin). A complete statistical reevaluation based on these measurement was performed. The analyses of efficacy in this report is based on the reevaluation of the external specialist.

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: 0.1 % mometasone furoate		

Statistical Methods (continued):

Statistical analyses

Primary Efficacy Analysis: Primary endpoint for this study was the non-inferiority of Mometasone cream (0.1 % mometasone furoate) to Ecural® Fettcreme using a non-inferiority margin Δ = 250 with respect to the AUC of change to baseline in infiltrate thickness, with a lower AUC being superior. The non-inferiority was assessed by the confidence interval method, comparing the upper one-sided confidence interval with coverage probability = 97.5 % (equal to upper two-sided confidence interval with coverage probability = 95.0 %) of the difference μT – μS in AUC to the non-inferiority margin Δ = 250. If the upper confidence interval was lower then the non-inferiority margin Δ, than the H_{01} had to be rejected in favor of the alternative H_{11}, which was the non-inferiority of Mometasone cream (0.1 % mometasone furoate) to Ecural® Fettcreme.

The non-inferiority analysis was performed on both efficacy analysis sets (ITT- and PP analyses). Both analyses should have led to similar conclusions for a robust interpretation.

Secondary efficacy analyses: The secondary endpoint of superiority of Mometasone cream (0.1 % mometasone furoate) to the active ingredient-free vehicle to Mometasone cream with respect to the AUC of change to baseline in infiltrate thickness was assessed by the confidence interval method, comparing the upper one-sided confidence interval (coverage probability = 97.5 %) of the difference $\mu_T - \mu_V$ in AUC to the origin. If the upper confidence interval was below 0, then the H_{02} had to be rejected in favor of the alternative H_{12}, which was the superiority of Mometasone cream (0.1 % mometasone furoate) to active ingredient-free vehicle.

The superiority analysis was performed on both efficacy analysis sets, with a priority on the ITT analysis and with the PP analysis being supportive.

All additional efficacy analyses were based on both efficacy analysis sets. The additional secondary endpoints were

- sonographic measurements of infiltrate thickness and changes to baseline in infiltrate thickness
- clinical assessment scores for assessment of efficacy

Descriptive statistics (valid n, mean, standard deviation, median, minimum and maximum) were calculated for the infiltrate thickness and the change to baseline in infiltrate thickness by treatment and test point.

Clinical assessment scores were descriptively evaluated. The scores were presented in frequency tables for each test point as well as the pooled total effect over all test points (sum of the clinical assessment scores assessed on days 4, 8 and 12, by patient). Score sums for clinical assessment were also calculated for the pooled total effect over the study period. The antipsoriatic efficacy was derived from the frequency of scores and score sums.

The calculated AUC was summarized by treatment using descriptive statistics (N, mean, standard deviation, median, min, max).

Infiltrate thickness and change to baseline in infiltrate thickness were summarized by treatment using descriptive statistics (N, mean, standard deviation, median, min, max). The mean change from baseline was given in percent.

Safety analyses: Adverse events including narrative description of skin irritation in the treatment areas and skin irritation outside the treatment area; were summarized descriptively, photographs were taken of local adverse events. Tables with adverse events were presented as appropriate.

Vital signs were summarized by time point with mean, standard deviation, median, minimum and maximum.

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: 0.1 % mometasone furoate		

Summary, conclusions:

Efficacy results:

Mometasone cream (0.1 % mometasone furoate) demonstrated a strong positive effect in the treatment of psoriasis in this psoriasis plaque test. The antipsoriatic effect of Mometasone cream (0.1 % mometasone furoate) was comparable to the effect seen for the comparator Ecural® Fettcreme on the basis of the sonographic measurements.

In the inferential analyses of the AUC of change to baseline in infiltrate thickness non-inferiority of Mometasone cream (0.1 % mometasone furoate) vs Ecural® Fettcreme could be shown. The upper confidence interval (68.8) was lower then the inferiority margin delta = 250.

The nearly identical mean percent reductions in infiltrate thickness after 12 days of treatment with Mometasone cream (0.1 % mometasone furoate) and Ecural® Fettcreme (-70.16 % and -70.53%, respectively) as well as the similar mean AUC values (-2037.0 and -1981.3, respectively) underlined the comparability of both formulations.

No relevant antipsoriatic effect was noted for the active ingredient-free vehicle. After 12 days of treatment with the active ingredient-free vehicle a percent reduction of 1.59 % was noted and the AUC was clearly higher than for the two active formulations (-47.1). The superiority of Mometasone cream (0.1 % mometasone furoate) to the active ingredient-free vehicle with respect to the AUC of change to baseline in infiltrate thickness was proven since the upper confidence interval of the difference of these two formulations (-1719.8) was below 0.

The data of the global clinical assessment supported the results of the sonographic measurements. Clear comparable clinical improvement was seen for both, Mometasone cream (0.1 % mometasone furoate) and Ecural® Fettcreme. No clinical improvement was seen for the active ingredient-free vehicle.

Safety results:

Only one non-serious AE (diarrhea), which was considered to be unlikely related to the study medication was reported in this study and the final physical examination did not show relevant findings in any of the subjects. The dermal tolerability was good and comparable for all study preparations even under the occlusive conditions in this study.

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: 0.1 % mometasone furoate		

Summary, conclusions (continued):

Conclusion:

A strong antipsoriatic effect which was comparable to the marketed Ecural® Fettcreme was found for Mometasone cream (0.1 % mometasone furoate) after 12 days occlusive treatment on the basis of the sonographic measurements. A relevant, clear and nearly identical reduction in the mean infiltrate thickness and similar mean AUC values were noted in the test fields treated with both 0.1 % mometasone furoate-containing formulations. This was also confirmed by the clinical assessment data.

The non-inferiority of Mometasone cream (0.1 % mometasone furoate) to Ecural® Fettcreme with respect to the AUC of change to baseline in infiltrate thickness could be shown.

No relevant antipsoriatic effect was noted for the active ingredient-free vehicle. The superiority of Mometasone cream (0.1 % mometasone furoate) to the active ingredient-free vehicle with respect to the AUC of change to baseline in infiltrate thickness was proven.

Only one non-serious AE which was considered to be unlikely related to the study medication was reported. There were no relevant observations related to safety in this study.

Date of the report: February 05, 2009