Clinical Study Report

Sponsor:	Almirall Hermal GmbH
Study no.:	H 530 000 – 0707 / 270404BS
EudraCT-no.:	2007-004287-46
Title:	A single-center, randomized, controlled, observer-blind study to determine the bioavailability of a topical corticosteroid formulation with mometasone in a vasoconstrictor assay in subjects with healthy skin
Study preparation:	**Study preparations:** 1) Mometason Salbe (Rez. 112), 0.1 % mometasone furoate (class III)) 2) Active ingredient-free vehicle to Mometason Salbe [Mometason Salbe Placebo (Rez. 113)] **Comparators:** Comparator 1 (Triamgalen® Salbe, class II, lower strength) Comparator 2 (Ecural® Salbe, class III, similar strength) Comparator 3 (Dermoxin® Salbe, class IV, higher strength) Two untreated control fields (one on each arm)
Clinical phase:	I
Description:	Altogether 30 caucasian male or female volunteers demonstrating adequate vasoconstriction to the corticosteroids (responders), aged 18 years or older with healthy skin, were included in this vehicle-controlled, observer-blind study. There were no dropouts. Data from 30 subjects were valid for analysis. Treatments were randomly assigned to the test fields. The test fields were compared intraindividually. Altogether seven test fields were evaluated. Four test fields were located on one volar forearm and three on the other. Per subject the active study preparation, the corresponding vehicle and three comparators of lower, similar and higher strength were tested. Two untreated test fields, one on each arm, served as controls. A single non-occlusive application of each formulation was performed for 6 hours. Chromametric measurements and clinical assessments were performed at baseline (prior to treatment) and 1, 2, 4, 6 and 18 hours after the end of the treatment period.
Principal Investigator:	[redacted] bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany
Clinical Trial Manager:	[redacted] Almirall Hermal GmbH Scholtzstrasse 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:	December 04 to 15, 2007
Date of Report:	February 26, 2008

2. Synopsis

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 0.1 %		

Title of Study:
A single-center, randomized, controlled, observer-blind study to determine the bioavailability of a topical corticosteroid formulation with mometasone in a vasoconstrictor assay in subjects with healthy skin

Investigator(s):
[redacted]

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

Publication (reference):
Not applicable to this study

Studied period (years):	Phase of development:
2007	I

Objectives:
Evaluation of blanching to assess the bioavailability of topical corticosteroid formulations

Methodology:
Single topical non-occlusive application for 6 hours to test fields (2 cm²) located on the volar surface of the forearms. Altogether seven test fields per subject. Skin color in the treated and untreated test fields was measured using chromametry. In addition, the degree of vasoconstriction was clinically assessed in the test fields compared to the untreated test fields.

Chromametric measurements and clinical assessments were performed at baseline and 1, 2, 4, 6 and 18 hours after the end of the treatment period.

Number of subjects (planned and analyzed):
Thirty male or female subjects were planned. There were no dropouts. Data from 30 subjects were valid for analysis.

Diagnosis and main criteria for inclusion:
Subjects with healthy skin in the area of the test fields, demonstrating adequate vasoconstriction to corticosteroids (responders), aged 18 years or older.

Test product(s), dose and mode of administration, batch number:
Mometason Salbe (Rez.112), 0.1 % mometasone furoate (class III), batch no. 744KK04
Mometason Salbe Placebo (Rez. 113), batch no. 745KK00

Single topical non-occlusive application of approx. 50 µl per test field (2 cm²)

Duration of treatment:
6 hours ± 10 minutes

Reference therapy or controls, dose and mode of administration, batch number:
Comparator 1 (Triamgalen® Salbe, class II, lower strength), batch no. 072K72
Comparator 2 (Ecural® Salbe, class III, similar strength), batch no. 5UHKKA88
Comparator 3 (Dermoxin® Salbe, class IV, higher strength), batch no. C31K8739
Two untreated control fields (one on each arm)

Single topical non-occlusive application of approx. 50 µl per test field (2 cm²)

Duration of treatment:
6 hours ± 10 minutes

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 0.1 %		

Criteria for evaluation:

Efficacy: Blanching was evaluated by chromametric measurement (a*) of skin redness (primary variable) and clinical assessment by scoring (secondary variable).

Safety: Medical history, screening and final clinical examination, recording of adverse events.

Statistical Methods:

Vasoconstriction properties were determined by evaluation of the degree of blanching in the test fields.
The primary efficacy variable was the area under the time curve of the baseline-corrected, untreated control-site corrected a-values.
Clinical assessment scores for degree of vasoconstriction were recorded as a secondary variable.
No hypotheses were generated.
The chromametric a-value measurements were identified as $\mathbf{a_{SN,\,FT,\,AP}}$, where

SN = subject number
FT = field type ($UNT_{(A)}$, $UNT_{(V)}$, T, V, C1, C2, C3)
T = treatment (Mometasone formulation)
V = vehicle
C1 = lower strength comparator (Triamgalen® Salbe)
C2 = similar strength comparator (Ecural® Salbe)
C3 = higher strength comparator (Dermoxin® Salbe)
AP = assessment point (T0: baseline, T1, T2, T4, T6 and T18: 1, 2, 4, 6 and 18 hours after treatment)

For each test field and assessment point baseline adjustments were made as

$$\mathbf{a^{bc}_{SN,\,FT,\,TP} = a_{SN,\,FT,\,T0} - a_{SN,\,FT,\,TP}}$$

These a^{bc} values were referred to as baseline-corrected a-values.

For each treated test field and each assessment point the baseline-corrected a-values were corrected for the baseline-adjusted untreated control site from the same arm.

$$\mathbf{a^{*}_{SN,\,FT,\,TP} := a^{bc,ucsc}_{SN,\,FT,\,TP} = a^{bc}_{SN,\,FT,\,TP} - a^{bc}_{SN,\,UNT(x),\,TP}}$$

These baseline-corrected, untreated control site-corrected a-values ($a^{bc,ucsc}$) were referred to as a*-values.
For each treatment the area under the time curve was calculated for the a*-values using the trapezoid rule:

$$A_{SN,FT} = (a^{*}_{SN,FT,T1} + a^{*}_{SN,FT,T2}) / 2 + (a^{*}_{SN,FT,T2} + a^{*}_{SN,FT,T4}) + (a^{*}_{SN,FT,T4} + a^{*}_{SN,FT,T6}) + (a^{*}_{SN,FT,T6} + a^{*}_{SN,FT,T18}) * 6$$

Statistical analysis: The hierarchical approach was performed for both active study preparations and corresponding active ingredient-free vehicles. With this ordered test procedure the overall significance level of 5 % could be kept.

For the cardinally-scaled original a-values and the derived a*-values as well as for the area under the curve descriptive statistics (valid n, mean, standard deviation, minimum and maximum) were presented by treatment and test point.

Clinical assessment scores were descriptively evaluated. The scores were presented in frequency tables. Score sums were also calculated.

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 0.1 %		

Summary, conclusions:

Efficacy results:

Under the conditions in this vasoconstrictor assay the topical bioavailability of Mometason Salbe (Rez. 112) was shown by a strong blanching effect. Clear blanching was also seen for the comparators Ecural® Salbe and Dermoxin® Salbe. Less but also clear blanching was observed for Triamgalen® Salbe. The active ingredient-free vehicle to Mometason Salbe [Mometason Salbe Placebo (Rez. 113)] had no relevant blanching effect.

The chromametric measurements demonstrated clear reduction in skin redness for Mometason Salbe (Rez. 112) and the reference products Ecural® Salbe and Dermoxin® Salbe. The maximum mean $a^{bc,ucsc}$-value of Mometason Salbe (Rez. 112) was 3.41. A similar reduction in skin redness was observed for the comparators Ecural® Salbe and Dermoxin® Salbe (mean $a^{bc,ucsc}$-values: 3.34 and 3.63, respectively). A lower maximum mean abc,ucsc-value of 2.18 was noted for Triamgalen® Salbe. Mean $a^{bc,ucsc}$-values just above zero indicated that Mometason Salbe Placebo (Rez. 113) had no blanching effect.

Similar mean AUCs were noted for Mometason Salbe (Rez. 112), Ecural® Salbe and Dermoxin® Salbe (43.99, 43.30 and 48.44, respectively). A lower mean AUC value of 27.92 was noted for Triamgalen® Salbe. No to minimal blanching was noted in the fields treated with the Mometason Salbe Placebo (Rez. 113) (mean AUC: 4.43).

In the statistical analyses the lower 95 % confidence limits of the AUC of Mometason Salbe (Rez. 112) Triamgalen® Salbe, Ecural® Salbe and Dermoxin® Salbe were greater than zero. Therefore it could be concluded that these four preparations were effective with respect to blanching. Furthermore, it was shown that Mometason Salbe (Rez. 112) was more effective than Mometason Salbe Placebo (Rez. 113).

Non-inferiority of Mometason Salbe (Rez. 112) to the comparators of lower strength (Triamgalen® Salbe), similar strength (Ecural® Salbe) and higher strength (Dermoxin® Salbe) could be demonstrated in all three cases considering a 20 % margin.

In general, the clinical assessment reflected the results of the chromametric data. Intense and moderate vasoconstriction was noted in the test fields treated with Mometason Salbe (Rez. 112) Ecural® Salbe and Dermoxin® Salbe in most of the subjects and in the test fields treated with Triamgalen® Salbe in half of the subjects. In the test fields treated with Mometason Salbe Placebo (Rez. 113) the majority of the subjects demonstrated no vasoconstriction.

Safety results:

Three nonserious adverse events were reported in three subjects in this study. The intensity was assessed as mild in one subject and as moderate in two subjects. The relationship to study medication was considered to be probable in one subject [reddening in the test field treated with Mometason Salbe Placebo (Rez. 113)] and as unlikely or not related in the other two subjects.

There were no other observations related to safety in this study. The final physical examination at the end of the study did not show relevant findings in any of the subjects.

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 0.1 %		

Summary, conclusions (continued):

Conclusion:

Under the conditions in this vasoconstrictor assay Mometason Salbe (Rez. 112) showed a strong blanching effect. The topical bioavailability of Mometason Salbe (Rez. 112) was shown by chromametric measurement and clinical assessment.

As expected it was shown that Mometason Salbe (Rez. 112) was more effective than its corresponding vehicle [Mometason Salbe Placebo (Rez. 113)].

The blanching effect of Mometason Salbe (Rez. 112) was comparable to the effect of Ecural® Salbe (potency class III) and Dermoxin® Salbe (potency class IV). Less but also a clear blanching was noted for the comparator Triamgalen® Salbe (potency class II).

In this study it could be shown that the bioavailability of the active ingredient mometasone furoate (0.1 %) was similar for the two different formulations Mometason Salbe (Rez. 112) and Ecural® Salbe.

There was one local mild AE which was probably related to the study medication. Reddening was reported in the test field treated with Mometason Salbe Placebo (Rez. 113). Two further nonserious AEs were reported which were considered to be unlikely or not related to study medication. There were no other observations related to safety in this study.

Date of the report: February 26, 2008