Clinical Study Report

Sponsor: Almirall Hermal GmbH

Study no.: **H 527000 – 0714 / 270405BS**

EudraCT-no.: **2007-007828-18**

Title: A single-center, randomized, vehicle-controlled, observer-blind study to determine the bioavailability of topical corticosteroid cream formulations with mometasone in a vasoconstrictor assay (pilot and main study) in subjects with healthy skin

Study preparation:

1. Mometasone cream 1 Rez. (061), 0.1 % mometasone furoate (class III)
2. Mometasone cream 2 Rez. (722), 0.1 % mometasone furoate (class III)
3. Active ingredient-free vehicle to Mometasone cream 1 (061)
4. Active ingredient-free vehicle to Mometasone cream 2 (722)

(2 creams and 2 corresponding vehicles in pilot study, one cream and corresponding vehicle in confirmatory study)

Comparators:

1. Triamgalen® Creme (class II, lower strength)
2. Ecural® Fettcreme (class III, similar strength)
3. Dermoxin® Creme (class IV, higher strength)

as well as one untreated control field on each arm.

Clinical phase: I

Description: Altogether 42 (pilot study: 12 volunteers, main study: 30 volunteers) 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 was one dropout in the main study who was replaced. Data from 42 subjects were valid for analysis. Treatments were randomly assigned to the test fields. The test fields were compared intraindividually. Altogether nine test fields were evaluated in the pilot study and seven in the main study. In the pilot study five test fields were located on the left volar forearm and four on the right while in the main study four test fields were located on the left volar forearm and three on the right. Two active study preparations, the corresponding active ingredient-free vehicles and three comparators of different strengths were tested in the pilot study. In the confirmatory part only one active study preparation and the corresponding active ingredient-free vehicle 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 per study phase. 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.

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GCP Compliance: The study was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.

Study dates: April 02 – May 16, 2008

Date of Report: July 1, 2008

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: Mometasone furoate 0.1 %		

Title of Study:
A single-center, randomized, vehicle-controlled, observer-blind study to determine the bioavailability of topical corticosteroid cream formulations with mometasone in a vasoconstrictor assay (pilot and main study) 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:
2008	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 nine test fields per subject in the pilot study and seven test fields per subject in the main study. 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):
Twelve subjects (male or female) were planned for the pilot study and 30 subjects for the main study. There was one dropout in main study who was replaced. Data from 42 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:
1. Mometasone cream 1 (061), 0.1 % mometasone furoate (class III), batch no. 809K02
2. Mometasone cream 2 (722), 0.1 % mometasone furoate (class III), batch no. 805KK01 (pilot study), 805KK02 (main study)
3. Active ingredient-free vehicle to Mometasone cream 1 (061), batch no. 805K01, 809K02
4. Active ingredient-free vehicle to Mometasone cream 2 (722), batch no. 805KK01 (pilot study), 805KK02 (main study)

(2 creams and 2 corresponding vehicles in pilot study, one cream and corresponding vehicle in main study)
Single topical non-occlusive application of approx. 50 µl per test field (2 cm²)

Duration of treatment:
6 hours ± 10 minutes

2. Synopsis (continued)

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

1. Triamgalen® Creme (class II, lower strength), batch no.: 074k52 (pilot study), 081K12 (main study)
2. Ecural® Fettcreme (class III, similar strength), batch no.: 7NGFA95002 (screening) 7NGKFA65 (pilot study), 7NGKFA95 (main study)
3. Dermoxin® Creme (class IV, higher strength), batch no.: C32K8496(pilot study), C34K1381 (main study)

as well as one untreated control field on each arm.
Single topical non-occlusive application of approx. 50 µl per test field (2 cm²)

Duration of treatment:
6 hours ± 10 minutes

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 (AUC) 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

$$a_{SN,\,FT,\,AP}$$

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® Creme)
C2 = similar strength comparator (Ecural® Creme)
C3 = higher strength comparator (Dermoxin® Creme)
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

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

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.

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

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

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

2. Synopsis (continued)

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Statistical Methods (continued):

Statistical analysis

Pilot study part: For the cardinally-scaled a^{bc}-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. These descriptive statistics were used to determined the formulations (active and vehicle) to be used in the confirmatory part.

Confirmatory study part: For the cardinally-scaled a^{bc}-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.

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

Summary, conclusions:

Efficacy results:

Under the conditions in the present vasoconstrictive assay (pilot and main study) the topical bioavailability of Mometasone cream 2 (Rez. 722) was shown by a strong blanching effect. Less but also clear blanching was observed for Mometasone cream 1 (Rez. 061) in the pilot study. On the basis of the results of the pilot study the sponsor decided to continue with the Mometasone cream 2 (Rez. 722) in the main study. The results of the pilot study were confirmed in the main study.

The blanching effect of Mometasone cream 2 (Rez. 722) was comparable to the strong effect seen for the comparators Ecural® Creme and Dermoxin® Creme. The blanching effect of Mometasone cream 1 (Rez. 061) was comparable to the effect seen for Triamgalen® Creme which was clear but less than the effect of the other comparators. The active ingredient-free vehicles to Mometasone cream 2 (Rez. 719) and Mometasone cream 1 (Rez. 058) had no relevant blanching effect.

The chromametric measurements demonstrated clear reduction in skin redness for Mometasone cream 2 (Rez. 722) and the reference products Ecural® Creme and Dermoxin® Creme. The maximum mean $a^{bc,ucsc}$-value of Mometasone cream 2 (Rez. 722) was 3.52 in the pilot study and 3.62 in the main study. A similar reduction in skin redness was observed for the comparators Ecural® Creme and Dermoxin® Creme (pilot study: mean $a^{bc,ucsc}$-values: 3.82 and 3.18, respectively; main study: mean $a^{bc,ucsc}$-values: 3.80 and 3.62, respectively). Lower maximum mean $a^{bc,ucsc}$-value were noted for Mometasone cream 1 (Rez. 061) (pilot study: mean $a^{bc,ucsc}$-values: 2.26) and for Triamgalen® Creme (pilot study: mean $a^{bc,ucsc}$-value: 2.66, main study: mean $a^{bc,ucsc}$-values: 2.35). Mean $a^{bc,ucsc}$-values just above zero indicated that vehicles to Mometasone cream 2 (Rez. 719) and Mometasone cream 1 (Rez. 058) had no blanching effect.

Similar mean AUCs were noted for Mometasone cream 2 (Rez. 722), Ecural® Creme and Dermoxin® Creme (pilot study: 44.51, 48.45 and 41.64, main study: 45.57, 46.95 and 49.55, respectively). Lower mean AUC values were noted for Mometasone cream 1 (Rez. 061) (pilot study: 28.99) and Triamgalen® Creme (pilot study: 33.84, main study: 30.08). No to minimal blanching was noted in the fields treated with the vehicles to Mometasone cream 2 (Rez. 719) (pilot study: mean AUC = 9.46, main study: mean AUC = 0.11) and Mometasone cream 1 (Rez. 058) (pilot study: mean AUC = 5.17).

2. Synopsis (continued)

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Summary, conclusions (continued):

Efficacy results (continued): In the statistical analyses the lower 95 % confidence limits of the AUC of Mometasone cream 2 (Rez. 722), Mometasone cream 1 (Rez. 061) Triamgalen® Creme, Ecural® Creme and Dermoxin® Creme were greater than zero. Therefore it could be concluded that these five preparations were effective with respect to blanching.

In the hierarchical testing (main study) it was shown that Mometasone cream 2 (Rez. 722) was more effective than the vehicle to Mometasone cream 2 (Rez. 719). Non-inferiority of Mometasone cream 2 (Rez. 722) to the comparators of lower strength (Triamgalen® Creme), similar strength (Ecural® Creme) could be demonstrated in all three cases considering a 20 % margin. Non inferiority to the higher strength comparator Dermoxin® Creme could not be confirmed for Mometasone cream 2 (Rez. 722).

In general, the clinical assessment reflected the results of the chromametric data. Intense to moderate vasoconstriction was noted in the test fields treated with Mometasone cream 2 (Rez. 722), Ecural® Creme and Dermoxin® Creme in nearly all subjects and in the test fields treated with Mometasone cream 1 (Rez. 061) and Triamgalen® Creme in more than half of the subjects. In the test fields treated with the vehicles to Mometasone cream 2 (Rez. 719) and Mometasone cream 1 (Rez. 058) the majority of the subjects demonstrated no vasoconstriction.

Safety results:

There were no adverse events or 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.

Conclusion:

Under the conditions in the present vasoconstrictive assay (pilot and main study) the topical bioavailability of Mometasone cream 2 (Rez. 722) was shown by a strong blanching effect. Less but also clear blanching was observed for Mometasone cream 1 (Rez. 061) in the pilot study.

On the basis of the results of the pilot study the sponsor decided to continue with Mometasone cream 2 (Rez. 722) in the main study. In the pilot study Mometasone cream 2 (Rez. 722) demonstrated stronger vasoconstriction than Mometasone cream 1 (Rez. 061). The results of the pilot study were confirmed in the main study.

The strong blanching effect of Mometasone cream 2 (Rez. 722) was comparable to the effect of Ecural® Creme (potency class III) and Dermoxin® Creme (potency class IV) (pilot and main study). The blanching effect of Mometasone cream 1 (Rez. 061) (pilot study) was comparable to the effect seen for Triamgalen® Creme (potency class II), which was clear but less than the other comparators. The topical bioavailability of all active formulations was shown by chromametric measurement and clinical assessment.

As expected no relevant blanching effect was seen for the active ingredient-free vehicles to Mometasone cream 2 (Rez. 719) and Mometasone cream 1 (Rez. 058).

The hierarchical testing of the main study results showed that the bioavailability of the active ingredient mometasone furoate (0.1 %) was similar for the two different mometasone formulations Mometasone cream 2 (Rez. 722) and Ecural® Creme. Furthermore, it was shown that Mometasone cream 2 (Rez. 722) was more effective than its corresponding vehicle (Rez. 719).

There were no AEs or other observations related to safety in this study.

Date of the report: July 1, 2008