Clinical Study Report

Sponsor:	Hermal
Study no.:	**H52700-0611 / 260612BS**
EudraCT-no.:	2006-003598-28
Title:	Pilot-Study for determination of bioavailability of topical corticosteroid formulations with mometasone in a vasoconstrictor assay
Study preparations:	**Study preparations with mometasone (potency class III):** Mometasone cream 1 (273), mometasone-furoate 0.1 % Mometasone cream 2 (282), mometasone-furoate 0.1 % Mometasone cream 3 (296), mometasone-furoate 0.1 % Mometasone ointment 1 (56), mometasone-furoate 0.1 % Mometasone ointment 2 (61), mometasone-furoate 0.1 % Mometasone emulsion 1 (603), mometasone-furoate 0.1 % **Comparators:** Ecural® Fettcreme (1 mg/g mometasone furoate) Ecural® Salbe (1 mg/g mometasone furoate)
Clinical phase:	I
Objectives:	Evaluation of blanching to assess the bioavailability of topical corticosteroid formulations
Description:	Altogether 12 male and female volunteers demonstrating adequate vasoconstriction to the corticosteroids (responders), aged 18 years or older with healthy skin, were included in this controlled, observer-blind study. There were no dropouts. Data from all 12 subjects were valid for analysis. Treatments were randomly assigned to the test fields. The test fields were compared intraindividually. Altogether ten test fields were evaluated, five on each volar forearm. Per subject six mometasone-formulations and two comparators of similar 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 Institute for Dermatological Research and Development GmbH Seydelstrasse 18, D-10117 Berlin, Germany
ClinicalTrial Manager:	[redacted] Hermal Scholtzstrasse 3, D-21465 Reinbek, Germany
GCP Compliance:	yes
Study dates:	November 27 to December 1, 2006
Date of Report:	February 05, 2007

2. Synopsis

Name of Company: Hermal	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		

Title of Study:	Pilot-Study for determination of bioavailability of topical corticosteroid formulations with mometasone in a vasoconstrictor assay
Investigator(s):	[redacted]
Study center(s):	bioskin Institute for Dermatological Research and Development GmbH, Berlin, Germany
Publication (reference):	Not applicable to this study
Studied period (years):	2006
Phase of development:	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 (2.0 cm²) located on the volar surface of the forearm. Altogether 10 test fields per subject including two untreated test fields, which served as controls. Skin color was measured using chromametry and the degree of vasoconstriction was clinically assessed at baseline and 1, 2, 4, 6 and 18 hours after the end of the treatment period.
Number of subjects (planned and analyzed):	Twelve male or female subjects were planned and included in the study. There were no dropouts. Data all 12 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:	**Study preparations with mometasone (potency class III):** Mometasone cream 1 (273), mometasone-furoate 0.1 %, batch no.: 643K01 Mometasone cream 2 (282), mometasone-furoate 0.1 %, batch no.: 643K01 Mometasone cream 3 (296), mometasone-furoate 0.1 %, batch no.: 643K01 Mometasone ointment 1 (56), mometasone-furoate 0.1 %, batch no.: 643K01 Mometasone ointment 2 (61), mometasone-furoate 0.1 %, batch no.: 643K01 Mometasone emulsion 1 (603), mometasone-furoate 0.1 %, batch no.: 643K01 single topical non-occlusive application of approx. 50 µl formulation per test field (2.0 cm²)
Duration of treatment:	6 hours ± 30 minutes
Reference therapy or controls, dose and mode of administration, batch number:	Ecural® Fettcreme (1 mg/g mometasone furoate), batch no.: 6NGFA54004 (screening), 6NGKFA36 Ecural® Salbe (1 mg/g mometasone furoate), batch no.: 6UHKA38002 (screening), 5UHKKA78 single topical non-occlusive application of approx. 50 µl formulation per test field (2.0 cm²)
Duration of treatment:	6 hours ± 30 minutes

2. Synopsis (continued)

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Criteria for evaluation:

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

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

Statistical Methods:

The chromametric a-value measurements were identified as

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

where

SN = subject number

FT = field type (UNT(A), UNT(V), S1, S2, S3, S4, S5, S6, C1, C2)

S1 – S6 = study preparations 1 – 6

C1 = comparator Ecural® Fettcreme

C2 = comparator Ecural® 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

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

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 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 study data were descriptively analyzed. No pre-defined hypotheses were tested.

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)

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Summary, conclusions:

Efficacy results: Under the conditions in this vasoconstrictor assay all six study preparations with 0.1 % mometasone-furoate showed a blanching effect, whereas the intensity in vasoconstriction differed. The two mometasone ointments (56 and 61) demonstrated the highest blanching effects among the study preparations. The intensity in blanching nearly reached the effect observed for the two comparators (Ecural® Fettcreme and Ecural® Salbe, potency class III). A lower blanching effect was observed for the mometasone cream (296). Less effective were the two mometasone creams (273) and (282) and the mometasone emulsion (603).

A maximum mean $a^{bc,ucsc}$-value of 2.43 was noted for mometasone ointment (56) and of 2.33 for the mometasone ointment (61). A lower reduction in skin redness was noted for the mometasone cream (296) (maximum mean $a^{bc,ucsc}$-value of 1.39). The lowest effects of comparable intense were noted for the mometasone creams (273) and (282) and the mometasone emulsion (603). The mean $a^{bc,ucsc}$-values were 1.06, 0.78 and 0.92, respectively. The highest reduction in skin redness was observed for the two comparators (Ecural® Fettcreme: 2.71, Ecural® Salbe: 2.94).

The highest mean AUC value of 33.21 among the study preparations was noted for the mometasone ointment (61), followed by the mometasone ointment (56) with a mean AUC value of 28.96. A lower mean AUC value of 21.37 was observed in the fields treated with for the mometasone cream (296). For the other three study preparations comparable lower AUC values were noted. The mean AUCs were 13.51 and 10.28 for the mometasone creams (273) and (282), respectively and 12.50 for the mometasone emulsion (603). The highest mean AUC values were noted for the two comparators (Ecural® Fettcreme: 38.02, Ecural® Salbe: 39.80).

In general the clinical assessment reflected the results of the chromametric data. Intense and moderate vasoconstriction was noted in the test fields treated with the two mometasone ointments (56 and 61) and the comparators in most of the subjects. Less intense vasoconstriction was seen for the mometasone cream (296). Mild or no vasoconstriction was noted in most of the subjects in the test fields treated with the other three study preparations (273, 603 and 282).

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 this vasoconstrictor assay a blanching effect of different intensity was observed for the six study preparations and the two comparators (Ecural® Fettcreme and Ecural® Salbe). The topical bioavailibility of mometasone-furoate was shown for all formulations by chromametric measurement and visual assessment.

The two mometasone ointments (56 and 61) demonstrated the highest reduction in skin redness among the study preparations and nearly reached the blanching effect observed for the two comparators (potency class III). A lower effect was observed for the mometasone cream (296). Less effective were the two mometasone creams (273 and 282) and the mometasone emulsion (603).

Although the mometasone-furoate formulations correspond to the Ecural® formulations regarding the active ingredient and concentration of active ingredient a similarity to these class III formulations could only be seen for the two mometasone ointments (56 and 61). The other pharmaceutical preparations were less effective.

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

Date of the report: February 05, 2007