Clinical Study Report

Sponsor:	**Hermal/BHI**
Study no.:	**250514BS / H 527 000 - 0519**
EudraCT-No.	**2005-004332-51**
Title:	Determination of bio availability of topical corticosteroid formulations in a vasoconstrictor assay
Study preparation:	**Group I:** **Study preparations:** Mometason cream (0,1 % mometasone-furoate, class III) Active ingredient-free vehicle to Mometason cream 0,1 % **Reference 1:** Dermatop® Creme (class II, lower strength) **Reference 2:** Ecural® Fettcreme (class III, similar strength) **Reference 3:** Dermoxin® Creme (class IV, higher strength) **Comparator 1:** Triamgalen® Creme **Comparator 2:** Advantan® Creme **Comparator 3:** Betagalen® Creme **Group II:** **Study preparations :** Mometason ointment (0,1 % mometasone-furoate, class III) Active ingredient-free vehicle to Mometason ointment 0,1 % **Reference 4:** Dermatop® Salbe (class II, lower strength) **Reference 5:** Ecural® Salbe (class III, similar strength) **Reference 6:** Dermoxin® Salbe (class IV, higher strength) **Comparator 4:** Triamgalen® Salbe **Comparator 5:** Advantan® Salbe **Comparator 6:** Betagalen® Salbe
Clinical phase:	**I**
Description:	Altogether 60 caucasian male or female volunteers demonstrating adequate vasoconstriction to the corticosteroids (responders), aged 18 years or older with healthy skin, 30 subjects per group were included in this vehicle-controlled, observer-blind study. There were no dropouts. Data from 60 subjects were valid for analysis. Treatments were randomly assigned to the test fields. The test fields were compared intraindividually. Altogether six test fields were evaluated. Three test fields were located on one volar forearm and three on the other. Per subject the active study preparation, the corresponding vehicle, three references of lower, similar and higher strength and three 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.

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GCP Compliance: yes

Study dates: December 19, 2005 to January 13, 2006

Date of Report: April 10, 2006

2. Synopsis

Name of Company: **Hermal/BHI**	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:	Determination of bioavailability of topical corticosteroid formulations in a vasoconstrictor assay
Investigator(s):	[redacted]
Study center(s):	bioskin Institute for Dermatological Research and Development GmbH, Hamburg, Germany
Publication (reference):	Not applicable to this study
Studied period (years):	2006
Phase of development:	I
Objectives:	Evaluation of blanching to assess the bio availability of topical corticosteroid formulations
Methodology:	Single topical application for 6 hours to test fields (2.0 cm²) located on the volar surface of the forearm. Altogether 10 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. 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):	60 male or female subjects were planned. 30 subjects per group were included in the study. There were no dropouts. Data from 60 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:	**Group I:** **Study preparations:** Mometason cream (0.1 % mometasone-furoate (class III), batch no.: 541KK02 Active ingredient-free vehicle to Mometason cream 0.1%, batch no.: 541KK02 **Group II:** **Study preparations:** Mometason ointment (0.1 % mometasone-fuorate (class III), batch no.: 542KK02 Active ingredient-free vehicle to Mometason ointment 0.1%, batch no.: 542KK02 single topical non-occlusive application of approx. 50 µl formulation per test field (2.0 cm²)
Duration of treatment:	6 hours ± 30 minutes

(continued...)

2. Synopsis (continued)

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

Group I:

References and Comparators:

Reference 1 (Dermatop® Creme, class II, lower strength), batch no.: 40EK293
Reference 2 (Ecural® Fettcreme, class III, similar strength), batch no.: 05DK1135
Reference 3 (Dermoxin® Creme, class IV, higher strength), batch no.: C16K4963
Comparator 1 (Triamgalen® Creme), batch no.: 051K92
Comparator 2 (Advantan® Creme), batch no.: 529K97A
Comparator 3 (Betagalen® Creme), batch no.: 052K52

Group II:

References and Comparators:

Reference 4 (Dermatop® Salbe, class II, lower strength), batch no.: 41EK288
Reference 5 (Ecural® Salbe, class III, similar strength), batch no.: 05DK1429
Reference 6 (Dermoxin® Salbe, class IV, higher strength), batch no.: C16K4962
Comparator 4 (Triamgalen® Salbe), batch no.: 051K02
Comparator 5 (Advantan® Salbe), batch no.: 525K61A
Comparator 6 (Betagalen® Salbe), batch no.:053K08

single topical non-occlusive application of approx. 50 µl formulation per test field (2.0 cm²)

Duration of treatment:

6 hours ± 30 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:

Statistical analysis

The main study aim was to prove that the efficacy of the active study preparations was non-inferior to the corresponding references and comparators. Blanching, expressed as a*-values, was used as a measure for efficacy. The mean area under the time curve AUC for the a*-values reflecting the course of blanching over the measurement period was used. The purpose of the statistical analysis was to compare the efficacy of the active study preparations and their corresponding references. The difference between the treatments was estimated with a two-sided 90 % confidence interval corresponding to an upper one-sided 95 % confidence interval. Blanching was estimated separately for each of the treatments and presented with 95 % confidence intervals. The upper 95 % confidence interval was discussed in relation to the 20 % equivalence margin generally used in bioequivalence studies.

Comparison of blanching induced by the active study preparations and their vehicles was performed in a similar manner. The difference between the treatments was estimated with a two-sided 95 % confidence interval and compared to zero.

2. Synopsis (continued)

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A hierarchical approach was used in order to enable the comparison of the Mometason 0.1 % formulations with the active references. With this hierarchical approach a correction of the significance level was not necessary.

Comparisons of the Mometason 0.1 % formulation with three corresponding comparators formulations were based on descriptive methods. Non-inferiority of Mometason was not assessed against these comparators.

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

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

Summary, conclusions:

Efficacy results:

Under the conditions in this vasoconstrictor assay Mometason cream 0.1 % and Mometason ointment 0.1 % showed clear blanching. In contrast both corresponding vehicles showed no or only slight blanching. The comparisons between the Mometason 0.1 % formulations and the corresponding vehicles showed that the active formulations were more effective.

The comparators with similar (Ecural® formulations) or higher strength (Dermoxin® formulations) showed clearly higher blanching effects than the Mometason 0.1 % formulations. Similar or higher blanching effects were also noted for the comparators with lower strength (Dermatop® formulations).

The chromametric measurements demonstrated clear reduction in skin redness for all active formulations. The baseline-corrected untreated control site-corrected a-values ($a^{bc,ucsc}$) reflect the degree of blanching. The maximum mean $a^{bc,ucsc}$ -value of Mometason cream 0.1 % was 0.87. A higher reduction in skin redness was observed for the references Dermoxin® Creme and Ecural® Fettcreme (mean $a^{bc,ucsc}$ -values: 2.86 and 2.56). For Dermatop® Creme the maximum mean $a^{bc,ucsc}$ -value was 1.16.

The maximum mean $a^{bc,ucsc}$ -value of Mometason ointment 0.1 % was 1.51. A higher reduction in skin redness was observed for Dermoxin® Salbe, Dermatop® Salbe and for Ecural® Fettcreme (3.68, 3.09 and 3.17, respectively).

The AUC of the baseline-corrected untreated control site-corrected a-values AUC ($a^{bc,ucsc}$) reflects the course of blanching over the measurement period.

The mean AUC was similar for Mometason cream 0.1 % and Dermatop® Creme (12.31 and 15.86, respectively). Higher AUC values were observed in the fields treated with Ecural® Fettcreme and Dermoxin® Creme (32.94 and 40.87 respectively). For the three comparators Triamgalen® Creme, Advantan® Creme and Betagalen® Creme mean AUC values of 21.44, 18.13 and 25.39 were noted. The mean AUC for the vehicle to Mometason cream 0.1% was 1.65.

The mean AUC was lower for Mometason ointment 0.1 % (23.35) than for Dermatop® Salbe (37.78). Higher mean AUC values were observed in the fields treated with Ecural® Salbe and Dermoxin® Salbe (43.15 and 48.12, respectively). For the three comparators Triamgalen® Salbe, Advantan® Salbe and Betagalen® Salbe mean AUC values of 30.27, 34.46 and 28.85 were noted. The vehicle to Mometason ointment 0.1% led to a low mean AUC values of 4.08.

2. Synopsis (continued)

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The blanching effect of both Mometason 0.1%- and all comparator formulations was confirmed by the lower 95 % confidence limits which were greater than zero.

Non-inferiority of both Mometason 0.1% formulations to the corresponding comparator of lower strength (Dermatop® formulations) considering a 20 % margin could not be established. Therefore subsequent conclusions were not possible.

The clinical assessment reflects the results of the chromametric data. The Mometason 0.1% formulations had clearly lower effects than the three references and the comparators. The corresponding vehicles to the Mometason 0.1% formulations showed only a slight vasoconstrictive effect.

A clear distinction between the three reference products according to their expected strength was noted over the course of the measurement period. Both Mometason 0.1 % formulations showed a blanching effect that was clearly lower than the effect of the references and comparators.

Safety results:

Only one adverse event occurred during the study, the relationship to the study product was classified as unlikely. There were no observations related to safety in this study.

Conclusion:

In this study the topical bioavailability of the corticosteroid formulation Mometason cream 0.1% and Momateasone ointment 0.1% were compared with the corresponding active ingredient-free vehicle and three reference formulations of lower, similar and higher strength. Additional a comparisons to three further comparators of lower and higher strength was performed on descriptive methods.

Under the conditions in this vasoconstrictor assay both Mometason 0.1 % formulations showed a blanching effect. The topical bioavailibility of Mometasone-furoate was shown for both formulations by chromametric measurement and visual assessment.

As expected it was shown that the both Mometason 0.1 % formulations were more effective than their corresponding vehicles

The blanching effect of the Mometason 0.1 % formulations was lower than the effect of all references (Ecural®-, Dermatop®- and Dermoxin®- formulations) and comparators (Triamgalen®-, Advantan®- and Betagalen®- formulations). A clear distinction between the reference and comparator products according to their expected strength was noted over the course of the measurement period.

Since the Mometason 0.1 % formulations correspond to the Ecural® formulations regarding the active ingredient, concentration of active ingredient and pharmaceutical form (7) a similarity to this class III formulation was expected. This could not be confirmed.

The inferiority of the Mometason 0.1 % formulations might be caused by a variation of the additional ingredients.

Only one AE, classified as unlikely to the study product, and no other observations related to safety were observed in this study.

Date of the report: April 10, 2006