Clinical Study Report

Sponsor:	Almirall Hermal GmbH
Sponsor study no.:	H 527 000 – 0713
bioskin study no.:	270403BS
EudraCT-no.:	2007-007827-42
Title:	A single-center, randomized, controlled study, double-blind for the study preparations and observer-blind for the controls, to determine the dermal tolerability of a topical Mometasone cream formulation on intact skin following repeated application during a 21-day treatment period
Study preparation:	**Study preparations:** 1. Mometasone cream 2 (722), 0.1 % mometasone furoate (class III) 2. Active ingredient-free vehicle to Mometasone cream 2 (722) **Negative control:** Aqua demin. **Positive control:** 0.3 % Sodium dodecyl sulfate (SDS)
Clinical phase:	I
Description:	The study was double-blind for the study preparations and observer-blind for the controls with random assignment of the treatments to the test fields. The study was planned to perform in 33 male or female subjects with healthy skin to get at least 30 evaluable cases. There was one dropout. Data from all 33 subjects were valid for safety and ITT analyses. Data from 31 subjects were valid for PP analysis. All subjects of the PP analysis received all treatments. The test fields were compared intraindividually. Altogether four test fields with intact skin on the back were examined. The test fields were treated occlusive once daily with the study preparations and controls during a 21-day treatment period (18 treatments). Applications were performed from Mondays to Saturdays. On Sundays no application was performed. Clinical assessment of the test fields was performed on study days 2 to 6, 8 to 13, 15 to 20 and on study day 22.
Principal Investigator:	[redacted] bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany
Clinical Trial Manager:	[redacted] Almirall Hermal GmbH Scholtzstrasse 3, 21465 Reinbek, Germany
GCP Compliance:	The study was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Study dates:	May 19 to June 9, 2008
Date of Report:	January 14, 2009

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:		
Name of Active Ingredient: Mometasone furoate		

Title of Study: A single-center, randomized, controlled study, double-blind for the study preparations and observer-blind for the controls, to determine the dermal tolerability of a topical Mometasone cream formulation on intact skin following repeated application during a 21-day treatment period	
Investigator(s): [redacted]	
Study center(s): bioskin GmbH, Hamburg, Germany	
Publication (reference): Not applicable to this study	
Studied period (years): 2008	Phase of development: I
Objectives: Nonspecific, local irritating reactions of the study preparations will be evaluated on intact skin in subjects with healthy skin	
Methodology: Occlusive application of approximately 100 µl of study preparations and controls to test fields with intact skin using special test chambers once daily during a 21-day treatment period (18 treatments), applications were performed daily from Mondays to Saturdays, on Sundays no application was performed. Dermal reactions were clinically assessed using a score prior to renewed application on study days 2 - 21 and on study day 22.	
Number of subjects (planned and analyzed): Thirty-three male or female volunteers were included in the study. There was one drop out. Data from 33 subjects were valid for safety and ITT analyses. Data from 31 subjects were valid for PP analysis.	
Diagnosis and main criteria for inclusion: Subjects with healthy skin in the area of the test fields on which reddening could be easily recognized, aged 18 or older.	
Test product(s), dose and mode of administration, batch number: Mometasone cream 2 (722), 0.1 % mometasone furoate (class III), batch no.: 805KK03 Vehicle to mometasone cream 2 (722), batch no.: 805KK03 topical occlusive application of approx. 100 µl per test field (2.5 cm^2)	
Duration of treatment: 21 days (18 treatments)	
Reference therapy or controls, dose and mode of administration, batch number: **Negative control:** Aqua demin., batch no.: 174KK87 **Positive control:** 0.3% sodium dodecyl sulfate in water (SDS), batch no.: 747KK04 topical occlusive application of approx. 100 µl per test field (2.5 cm^2)	
Duration of treatment: 21 days (18 treatments)	

2. Synopsis (continued)

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Criteria for evaluation:

Efficacy: Nonspecific, local irritating reactions of the study preparations were evaluated on intact skin in subjects with healthy skin.

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

Statistical Methods:

Irritation scores from the individual assessment days:

Let $ERY_{SN,TRT,TP}$ was the erythema score assessed on the field treated with TRT in subject SN and on day TP (TP in {2,3,4,..,22}).

Cumulative irritation scores:

A cumulative irritation score (CIS) was calculated by day. For day X the CIS for erythema was calculated by adding up all previous assessment scores including day X, i.e.

$$CIS_{SN,TRT,X} = \sum_{i=1}^{X} ERY_{SN,TRT,i}$$

Cumulative irritation index:

To summarize the tolerability a cumulative irritation index was calculated using the sum of the cumulative irritation scores on day 22 for all subjects divided by a denominator:

For the erythema score we had:

$$CII_{TRT} = \frac{\sum_{j}^{SN} CIS_{j,TRT,22}}{4NX} \bullet 100\%$$

where N was the number of subjects with values and X the number of assessments (18).

Tolerability data were summarized by treatment and day using descriptive statistical methods. In addition to frequency tables, summaries were reported giving N, N(missing), mean, standard deviation, median, minimum and maximum.

The cumulative irritation score (by day) and the cumulative irritation index were reported giving N, mean, standard deviation, median, minimum and maximum.

Differences between the treatments were tested by the exact Wilcoxon-Signed Rank test at level $\alpha = 0.05$. Since this was an exploratory study no adjustment due to multiple testing was performed and the obtained p-values were only interpreted descriptively.

In case of deviating analysis sets, the reports were given for all analysis sets.

that was

$H_0: \theta = 0$ vs. $H_1: \theta \neq 0$

where θ is the subject-specific difference of the respective cumulative irritation score.

2. Synopsis (continued)

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Statistical Methods (continued):

The hypothesis was tested for the following treatment pairs:

Mometasone cream (mometasone furoate, 0.1 %)	vs.	Vehicle to mometasone cream
Mometasone cream (mometasone furoate, 0.1 %)	vs.	Aqua demin.
Vehicle to mometasone cream	vs.	Aqua demin.
Mometasone cream (mometasone furoate, 0.1 %)	vs.	Sodium Dodecyl Sulfate 0.3 %
Vehicle to mometasone cream	vs.	Sodium Dodecyl Sulfate 0.3 %

Summary, conclusions:

Tolerability results:

Under the present study conditions with occlusive topical application once daily over a 21-day study period mometasone cream (0.1 % mometasone furoate) was moderately tolerated.

For mometasone cream the maximum number of erythematous score 1 reactions occurred in 18 of 32 subjects (56.3 %) on study days 6 and 15. The maximum number of erythematous score 2 reactions were noted in 7 of 32 subjects (21.9 %) on study day 16. At the end of study (day 22) 28 of 32 subjects (87.6 %) did not show signs of clinically relevant skin irritations (score 0 and 1 reactions). Four subjects (12.5 %) showed score 2 reactions. No stronger reactions were observed for mometasone cream. The mean assessment score for erythema had its maximum on study day 16: 0.94 (SD = ± 0.72). The total score sum for days 2 - 22 was 337 of a possible maximum of 2316 expressed as the cumulative irritation index (CII): 337 / 2316 (14.6 %).

For the vehicle to mometasone cream the maximum number of erythematous score 1 reactions was shown in 12 of 32 subjects (37.5 %) at study day 6 and the maximum number of erythematous score 2 reactions in 7 of 32 subjects (21.9 %) at study day 8. At the end of study 31 of 32 subjects (96.9 %) did not show signs of clinically relevant skin irritation (score 0 and 1 reactions). No score 2 or 4 reactions were observed for the vehicle to mometasone cream. Only one subject demonstrated one score 3 reaction on study day 8 which led to discontinuation of treatment. The mean assessment score for erythema had its maximum on study day 8: 0.75 (SD = ± 0.92). The CII for days 2 – 22 was 228 / 2316 (9.8%).

In the test fields treated with the negative control (Aqua demin.) four score 1 reactions were observed in three subjects between study day 4 and 6. The cumulative irritation index (CII) was 4 / 2316 (0.2 %).

In the test fields treated with the positive control (0.3 % SDS) erythematous reactions were observed in all subjects. Treatments with the positive control were discontinued before the last scheduled treatment in all 32 subjects due to score 3 reactions. Score 3 was carried forward (LOCF) for all remaining assessment points. The cumulative irritation index (CII) was 1284 / 2316 (55.4 %).

The cumulative irritation score (CIS) of mometasone cream for day 22 was significantly higher compared to the corresponding vehicle ($p = 0.0289$) and the negative control ($p < 0.0001$), but significantly lower compared to the positive control ($p < 0.0001$).

The vehicle to mometasone cream showed a significant lower CIS for the positive control and a significant higher CIS for the negative control ($p < 0.0001$, each).

Safety results:

Altogether five non-serious adverse events were reported in four subjects. One AE was classified as moderate and the subject discontinued the study due to gastroenteritis. All other AEs were classified as mild. Four AEs were considered to be unlikely related and one AE was considered to be not related to the study medication. There were no other relevant observations related to safety in this study.

Conclusion:

The aim of the study was to investigate the dermal tolerability of a topical mometasone cream formulation in comparison to its vehicle.

Under the present study conditions with occlusive topical application once daily over a 21-day study period mometasone cream and its vehicle showed a mild to moderate irritative potential.

The maximum of erythematous score 1 reactions occurred in 56.3 % of the subjects treated with mometasone cream and in 37.5 % subject treated with the vehicle to mometasone cream on study day 6. Mometasone cream showed a second maximum (56.3 % of the subjects) on study day 16. The maximum of erythematous score 2 reactions were noted in 21.9 % of the subjects on study day 16 after treatment with mometasone cream and on study day 8 after treatment with vehicle to mometasone cream.

43.8 % of the subjects treated with mometasone cream and 21.9 % of the subjects treated with the respective vehicle showed score 1 reactions at the end of study. Score 2 reactions were noted in 12.5 % of subjects treated with mometasone cream. Only one subject demonstrated one score 3 reaction after treatment with vehicle to mometasone cream on study day 8. No other or stronger reactions were observed for mometasone cream and its vehicle, respectively.

For mometasone cream the mean assessment score for erythema had its maximum on study day 16: 0.94 (SD = ± 0.72) and for the vehicle of mometasone cream on study day 8: 0.75 (SD = ± 0.92).

The cumulative irritation score (CIS) of mometasone cream for day 22 was significantly higher compared to the corresponding vehicle ($p = 0.0289$).

Mometasone cream and its vehicle show the same number of maximum score 2 reactions, but in case of mometasone cream these reactions are longer persistent and occurred at a later timepoint. The corticosteroid may slow down the occurrence of reactions. Temporary score 1 reactions may be caused by occlusion effects or steroid initiated follicular reactions. Score 1 reactions which do not lead to cumulation (score 2 reactions) cannot be considered to be clinically relevant for non occlusive treatment as performed under normal clinical conditions.

The majority of reactions noted during and at the end of the study were score 1 reactions and occurred intermittently and did not show cumulative effects. Therefore the reaction potential cannot be considered as clinically relevant. Although the difference to the vehicle to mometasone cream is statistically significant this difference cannot be considered clinically relevant.

The majority of reactions noted during and at the end of the study were score 1 reactions and occurred intermittently and did not show cumulative effects. Therefore the reaction potential cannot be considered as clinically relevant. The difference between mometasone cream versus vehicle to mometasone cream is clinically not relevant.

Overall, the reactions of mometasone cream and its vehicle were comparable. They were both moderately tolerated and demonstrated a mild to moderate irritant potential under the conditions of the study.

In table 6 of section 14 it is shown that fourteen of all treated subjects were already treated once or more with corticosteroid in previous studies. A predisposition or sensitization of subjects can not be excluded after repetitive exposition. Therefore the data are to be qualified.

Five non-serious AEs were reported in this study which were considered to be unlikely or not related to the study medication. There were no other observations related to safety in this study.

Date of the report: January 14, 2009