2. Synopsis

Name of Company: **Hermal Kurt Herrmann GmbH & Co. OHG**	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Hydrocortisone-17-butyrate, 0.1 %		

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, Berlin, Germany
Publication (reference): Not applicable to this study

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

Objectives: Evaluation of blanching to assess the bioavailability of topical corticosteroid formulations
Methodology: Single topical non-occlusive application for 16 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 24 hours after the end of the treatment period.
Number of subjects (planned and analyzed): 30 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: **Study preparations:** Laticort Emulsion (0.1 % hydrocortisone-17-butyrate (class II), article no.: K0524/1 Active ingredient-free vehicle to Laticort Emulsion, article no.: K0524/3 Single topical non-occlusive application of approx. 50 µl per test field (2 cm²)
Duration of treatment: 16 hours ± 30 minutes
Reference therapy or controls, dose and mode of administration, batch number: **Comparators:** Comparator 1 (Betagalen® Lotion, class III, higher potency), article no.: K0195/09 Comparator 2 (Hydrogalen® Lotion, class I, lower potency), article no.: K0196/09 Comparator 3 (Alfason® Crelo, class II, similar potency), article no.: K0194/09 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: 16 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: Medical history, screening and final clinical examination, recording of adverse events.

Statistical Methods:

The main study aim was to prove that the efficacy of the active study preparation was non-inferior to the corresponding 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 preparation and the corresponding comparators. 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 preparation and the vehicle was performed in a similar manner. The difference between the treatments was estimated with a two-sided 95 % confidence interval and compared to zero.

A hierarchical approach was used in order to enable the comparison of the Hydrocortisone-17-butyrate, 0.1 % formulation with the active comparators. With this hierarchical approach a correction of the significance level was not necessary.

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) are presented.

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

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Summary, conclusions:

Efficacy results:

Under the conditions in this vasoconstrictor assay the topical bioavailability of Laticort Emulsion was shown by a clear blanching effect. Clear blanching was also seen for the comparators Betagalen® Lotion and Alfason® Crelo. Less effective was the Hydrogalen® Lotion that showed a very slight blanching effect. The vehicle to Laticort Emulsion showed no blanching.

The chromametric measurements demonstrated clear reduction in skin redness for Laticort Emulsion, Betagalen® Lotion, and Alfason® Crelo. The maximum mean a ^{bc,ucsc}-value of Laticort Emulsion was 2.82. A similar reduction in skin redness was observed for the comparators Betagalen® Lotion and Alfason® Crelo (mean a ^{bc,ucsc} -values: 2.34 and 2.56, respectively). A clearly lower maximum mean a ^{bc,ucsc} -value of 0.31 was noted for Hydrogalen® Lotion. No positive mean a ^{bc,ucsc} -values were noted for the vehicle to Laticort Emulsion over the study period.

The highest mean AUC of 28.85 was noted for Laticort Emulsion. Similar mean AUCs were noted for Betagalen® Lotion and Alfason® Crelo (28.22 and 27.12, respectively). For the Hydrogalen® Lotion a clearly lower mean AUC value of 5.71 was noted. The vehicle to Laticort Emulsion led to a negative mean AUC value of -2.46 indicating a slight increase in skin redness.

The statistical comparisons between the Laticort Emulsion and the corresponding vehicle showed that the active formulation was more effective since the lower 95 % confidence limits which were greater than zero.

Non-inferiority of Laticort Emulsion to the comparators of lower strength (Hydrogalen® Lotion), similar strength (Alfason® Crelo) and higher strength (Betagalen® Lotion) 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 Laticort Emulsion and the comparator Alfason® Crelo. Moderate and mild vasoconstriction was noted in the test fields treated with Betagalen® Lotion. In the test fields treated with Hydrogalen® Lotion most of the subjects demonstrated no vasoconstriction, mild vasoconstriction was noted only in a few subjects. The corresponding vehicle to Laticort Emulsion showed no vasoconstrictive effect.

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 Laticort Emulsion showed a clear blanching effect. The topical bioavailability of Laticort Emulsion was shown by chromametric measurement and visual assessment.

As expected it was shown that Laticort Emulsion was more effective than its corresponding vehicle.

The blanching effect of Laticort Emulsion was comparable to the effect of Alfason® Crelo (potency class II) and Betagalen® Lotion (potency class III). Less effective was the comparator Hydrogalen® Lotion (potency class I).

In this study it could be shown that the bioavailability of the active ingredient hydrocortisone-17-butyrate (0.1 %) was similar for the two different formulations Laticort Emulsion and Alfason® Crelo.

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

Date of the report: March 08, 2007