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 dermal tolerability of topical formulations on intact skin following repetitive non-occlusive application during a 21 day treatment period	
Investigator(s): [redacted]	
Study center(s): bioskin Institute for Dermatological Resarch and Development GmbH, Berlin, Germany	
Publication (reference): Not applicable to this study	
Studied period (years): 2007	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: Application of approximately 50 µl of study preparations and controls to test fields with intact skin once daily during a 21 day treatment period (18 treatments), applications were performed daily from Mondays to Saturdays, on Sundays no application was performed, test fields were covered with a breathable membrane. 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 were two drop outs. Thirty-one subjects were included in the 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: **Study preparations:** 1. Laticort Emulsion with hydrocortisone-17-butyrate, article no.: K0524/1 2. Active ingredient-free vehicle to Laticort Emulsion, article no.: K0524/3 Topical application of approximately 50 µl formulation per test field (2.0 cm²) once daily.	
Duration of treatment: 23 ± 1 hour for 21 days (18 treatments)	
Reference therapy or controls, dose and mode of administration, batch number: **Negative control:** Aqua demin., batch no.: K0957/11 **Positive control:** 0.3% sodium dodecyl sulfate in water (SDS), batch no.: K0956/11	
Duration of treatment: 23 ± 1 hour for 21 days (18 treatments)	

2. Synopsis (continued)

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Name of Active Ingredient: Hydrocortisone-17-butyrate, 0.1 %		

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 ERYSN,TRT,TP be 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) will be calculated by day. For day X the CIS for erythema is 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 will be calculated using the sum of the cumulative irritation scores on day 22 for all subjects divided by a denominator:
For the erythema score we have:

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

where N is the number of subjects with values and X the number of assessments (18).
Tolerability data will be summarized by treatment and day using descriptive statistical methods. In addition to frequency tables, summaries will be reported giving N, N(missing), mean, standard deviation, median, 68 % range, minimum and maximum.
The cumulative irritation score (by day) and the cumulative irritation index will be reported giving N, mean, standard deviation, median, 68 % range, minimum and maximum.
Differences between the treatments will be tested by the exact Wilcoxon-Signed Rank test at level α = 0.05. Since this is an exploratory study no adjustment due to multiple testing will be performed and the obtained p-values will only be interpreted descriptively.
In case of deviating analysis sets, the reports will be given for all analysis sets.

Summary, conclusions:

Dermal tolerability results:

For the ITT- and the PP- populations Laticort Emulsion (0.1 % hydrocortisone-17-butyrate) and the corresponding vehicle demonstrated a slight irritant potential whereby somewhat more intense erythematous reactions were seen for the active formulation Laticort Emulsion. The following conclusions are based on the PP-population since this population represents the most reasonable information:

After non-occlusive topical application once daily during a 21 day treatment period (18 treatments) Laticort Emulsion led to moderate erythema in 9 of 31 subjects whereby in 7 of these 9 subjects only one single score 2 reaction (clear, sharply demarcated erythema) was noted on the last study day (day 22). Furthermore, slight erythematous reactions were observed in 18 and no reactions were noted in 4 of the 31 subjects. The cumulative irritation index for days 2 - 22 was 233 / 2232 (10 %).

In the test fields treated with active ingredient-free vehicle to Laticort Emulsion slight erythematous reactions were observed in 25 subjects. The cumulative irritation index for days 2 - 22 was 135 / 2232 (6 %).

No statistical differences were found between the Laticort emulsion and the corresponding vehicle.

In the test fields treated with the negative control (Aqua demin.) isolated slight erythematous reactions were seen in six subjects over the entire study period. The cumulative irritation index for days 2 - 22 was 8 / 2232 (0 %).

The number and strength of reactions of the positive control (0.3 % SDS) were clearly less than expected. Only isolated slight erythematous reactions were seen in seven subjects over the entire study period. The cumulative irritation index for days 2 - 22 was 17 / 2232 (1 %). With hindsight, this lack of occurance and intensity of irritant reactions can be explained by the application procedure. Since the solution was applied non-occlusively the solvent evaporated. As for all surfactants, SDS can only exert irritant reactions in a dissolved form.

Safety results:

Altogether ten non-serious adverse events were reported in nine subjects. Six AEs were classified as mild and four as moderate. Eight AEs were considered to be unlikely related and two AEs were considered to be not related to the study medication. There were no other relevant observations related to safety in this study.

Conclusion:

Under the conditions in this study a slight irritant potential was seen after treatment with Laticort Emulsion and the corresponding vehicle. No statistical differences were found between the Laticort emulsion and the corresponding vehicle. Slight erythematous reactions were noted in the majority of the subjects after treatment with both formulations. More intense reactions were noted for the active formulation Laticort Emulsion, but most of these clear, sharply demarcated erythema reactions were noted only once on the last study day.

Overall, the Laticort Emulsion and the corresponding vehicle were well tolerated over the course of the study.

There were ten mild to moderate non-serious adverse events reported in nine subjects which were considered unlikely or not related to the study medication. The final physical examination did not show relevant findings in any of the subjects.

Date of the report: May 24, 2007