## 2. Synopsis

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| Name of Company:<br>Hermal Kurt Herrmann GmbH & Co. OHG | Individual Study Table Referring to Part of the Dossier<br><br>Volume:<br>Page: | *(For National Authority Use Only)* |
| Name of Finished Product:<br>Curatoderm® Emulsion | | |
| Name of Active Ingredient:<br>Tacalcitol | | |

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| Title of Study:<br>Evaluation of safety and efficacy of Curatoderm® Emulsion in the treatment of patients with mild to moderate plaque psoriasis | |
| Investigator(s):<br>[redacted] | |
| Study center(s):<br>bioskin Institute for Dermatological Research and Development GmbH, Hamburg/Berlin, Germany | |
| Publication (reference):<br>Not applicable to this study | |
| Studied period (years):<br>2006-2007 | Phase of development:<br>IIIb |
| Objectives:<br>The aim of this study was to evaluate the safety and efficacy of the antipsoriatic Curatoderm® Emulsion in patients with mild to moderate plaque type psoriasis vulgaris. | |
| Methodology:<br>Application of the study preparation Curatoderm® Emulsion to all psoriatic plaques once daily over a twelve week treatment period by the patients.<br>Parathormone and calcium levels in serum (albumine corrected calcium according to Payne) were evaluated at screening and on study days 57 and 85. The clinical skin condition of the psoriatic plaques was evaluated using the Psoriasis Area and Severity Index (PASI) at screening an on study days 1, 29, 57, 85, and 169. Blood chemistry, hematology, and urinalysis were evaluated at screening and on study day 85. Additionally, a questionnaire was filled out with the patients. | |
| Number of patients (planned and analyzed):<br>Sixty-three male or female patients were included in the study. Five patients dropped out of the study from which three patients were replaced. Sixty evaluable patients were included in the safety analysis and the ITT analysis. Fifty-eight patients were included in the PP analysis. | |
| Diagnosis and main criteria for inclusion:<br>Patients with mild to moderate psoriasis vulgaris aged 18 years or older. | |
| Test product(s), dose and mode of administration, batch number:<br>Curatoderm® Emulsion, batch no.: 627kk63<br>Topical application once daily on all psoriatic plaques, maximum 70 emulsion g per week. | |
| Duration of treatment:<br>Twelve weeks. | |
| Reference therapy or controls, dose and mode of administration, batch number:<br>Not applicable. | |

## 2. Synopsis (continued)

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Criteria for evaluation:

Primary safety:

As primary safety parameters parathormone (PTH intact) levels and Calcium levels in serum (calcium corrected according to Payne) were evaluated on screening and on study days 57 and 85.

Secondary efficacy:

The clinical skin condition of the psoriatic plaques was evaluated using the Psoriasis Area and Severity Index (PASI) at screening an on study days 1, 29, 57, 85, and 169. The PASI was based on the quantitative assessment of three typical signs of psoriatic lesions: erythema, scaling, and thickness, combined with the skin surface area involvement. PASI was calculated in order to evaluate the improvement of intensity of overall psoriasis severity and coverage. Additionally, a questionnaire was filled out with the patients

Secondary safety:

Blood chemistry, hematology, and urinalysis at screening and on study day 85, screening and final clinical examinations, recording of adverse events. Calcium and Creatinine levels in urine were determined at screening and on study day 57 and 85.

Statistical Methods:

Analysis of safety

Results of laboratory parameters were summarized by test point with descriptive statistics containing N, mean, median, standard deviation, range and quartiles. Shift tables were generated to assess the influence of the study preparation on parathormone and calcium levels. Changes in parathormone and calcium levels from baseline to week 12 were assessed using Student's paired t-test or the Wilcoxon matched pairs test as applicable.

The frequency distributions of the presence/absence of adverse events associated with topical application of the study medication were summarized by visit with frequency counts and percentages. No formal statistical hypothesis testing was performed.

All patients receiving study medication were included in the safety analyses. All adverse events reported during the study were listed, documenting course, severity, possible relationship to study drug, and outcome.

Analysis of efficacy

All efficacy analyses are secondary endpoints and were descriptively interpreted.

The clinical assessment of skin condition using the PASI and the change from baseline were summarized by visit with descriptive statistics containing N, mean, median, standard deviation, range and quartiles.

Changes from baseline were calculated as PASI at visit X minus PASI at baseline. Therefore, negative values indicated a decrease in PASI and an improvement of the study disease. Worsening of the study disease was indicated by positive values.

Student's paired t-test was used to compare the PASI at baseline with the post-baseline PASI if the data were normally distributed. Otherwise, the Wilcoxon matched pairs test was used for comparison. The obtained p-values were interpreted descriptively. No adjustment of p-values due to multiple comparisons was performed.

Analysis of questionnaire data

Questionnaire data were descriptively summarized. Absolute and relative frequencies were presented for categorical data.

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Summary, conclusions:

Primary safety and secondary efficacy results: In the present study treatment with Curatoderm® Emulsion revealed no pathological relevant influence on the calcium homeostasis when applied to all psoriatic plaques over a treatment period of three months.

The mean calcium (Payne) level in serum and the 95 % confidence limits were within the reference range during the whole study. No relevant change was noted for the mean calcium level (mean values constant at 2.1). The mean PTH - intact level and the 95 % confidence limits were in the reference range during the whole study. However, a slight increase for the mean PTH - intact level from 32.8 to 36.4 was noted. Although this slight increase was statistically significant it is considered to have no pathological relevance.

In patients treated with Curatoderm® Emulsion over a treatment period of three months psoriasis was significantly improved. A continuous decrease was seen for the mean Psoriasis Area and Severity Index (PASI) over the treatment period. The mean PASI decreased from 7.5 to 5.0 over the treatment period and slightly increase to 5.6 in the follow-up period. The decrease of the PASI was observed for all assessed time points compared to baseline and was statistically significant. Additionally, the questionnaire evaluations revealed a reduction of itching intensity.

Secondary safety results**:** During the study one SAE was noted that was considered to be not related to the study preparation. Further on, 65 non serious adverse events were reported in 32 patients. One adverse event led to discontinuation of the study because of worsening of itching. All other adverse events were of mild to moderate severity and were considered to be unlikely or not related to the study preparation. Five adverse events were based on increased laboratory values. The investigators considered all other laboratory values to be in an acceptable range for this study. Only slight changes in the mean hematological and mean clinical chemistry values were found between screening and the final visit.

Conclusion: The mean calcium (Payne) level in serum and the 95 % confidence limits were within the reference range during the whole study. No relevant change was noted for the mean calcium level (mean values constant at 2.1).The mean PTH - intact level and the 95 % confidence limits were in the reference range during the whole study. However, a slight but statistically significant increase for the mean PTH - intact level from 32.8 to 36.4 was noted. This increase is considered to be not related to treatment with Curatoderm® Emulsion because of the following: If Curatoderm® Emulsion would have had an influence on calcium homeostasis, calcium would have been increased (in this study the calcium level did not change). Consequently, due to regulatory effects of calcium homeostasis the PTH level would have been decreased (in this study PTH increased). Therefore, the noted slight increase of PTH is rather based on external factors (e. g. nutrition, UV exposure or physical exercises). It can be concluded that the increased mean PTH level in this study have no pathological relevance.

Curatoderm® Emulsion led to a significant improvement of psoriasis in the treated patients. A statistically significant decrease of the mean Psoriasis Area and Severity Index (PASI) was seen for all assessed time points over the treatment period. The mean PASI decreased from 7.5 on study day 1 to 5.02 at the end of the treatment period. Additionally, the questionnaire evaluations revealed a reduction of itching intensity.

There was one adverse event (worsening of itching) which was considered to be possibly related to Curatoderm® Emulsion. This patient had to discontinue the study. The other safety parameters revealed no safety concerns for the psoriatic patient population in this study.

Date of the report: September 04, 2007