# Clinical Study Report

# LEO 19123 Cream in the Treatment of Hand Eczema

**A Phase II, proof of concept study, testing once daily use of two dose-combinations of LEO 19123 cream (calcipotriol and LEO 80122) in the treatment of hand eczema**

An international, multi-centre, prospective, randomised, double-blind, 3 arm, vehicle-controlled, parallel group, 3 week phase II clinical study

## Synopsis

**LEO Pharmaceutical Products Ltd. A/S**
**(LEO Pharma A/S)**

**Medical Department**

**LEO 19123-C22**

**EudraCT Number: 2006-002686-39**

**18-Mar-2008**

# 1 CLINICAL STUDY REPORT APPROVAL FORM

## 1.1 APPROVAL STATEMENT

The following persons have approved this Clinical Study Report using electronic signatures as presented on the last page of this document.

[redacted], International Clinical Development, LEO

[redacted] Biostatistics Department, LEO HQ

## 1.2 APPROVAL STATEMENT INVESTIGATORS

On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report.

The International Co-ordinating Investigator

Dr. [redacted]

has approved this report as presented on the International Co-ordinating Investigator Clinical Study Report Approval Form adjoined as a separate page to this document.

# 2 REPORT STATEMENTS

## 2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports; E6 Good Clinical Practice; and E9 Statistical Principles for Clinical Trials).

## 2.2 STUDY AUTHENTICATION

LEO Pharma
Medical Department

GCP I-SOP 02

### AUTHENTICATION FORM

| Protocol Code Number: | Report Date (dd-mmm-yyyy): | FF Index No.: |
|---|---|---|
| LEO 19123-C22 | 21 Jan 2008 | 116.1 |

Report Title:
LEO 19123 cream in the treatment of hand eczema

This study was performed in compliance with the Good Clinical Practice (GCP) standard issued by the International Conference on Harmonisation (ICH), the Declaration of Helsinki with subsequent amendments, and respecting national rules/regulations.

The study was performed in accordance with the approved Study Protocol and with LEO Pharma Standard Operating Procedures for GCP. The report provides a true and accurate record of the results obtained.

Authorised by: PCPC

[redacted] [redacted]

Date 21 Jan 2008
dd-mmm-yyyy

# 3 SYNOPSIS

| | | |
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| Name of Sponsor/Manufacturer:<br>LEO Pharma A/S | Location of study report in Regulatory Dossier for authorities | |
| Name of Investigational Product/ Finished Product, if available:<br>Not applicable | Volume: | |
| Name of Active Substance:<br>Calcipotriol and LEO 80122 | Page: | |

Title of study/Protocol Code Number:
LEO 19123 Cream in the Treatment of Hand Eczema /LEO 19123-C22

International Co-ordinating Investigator:
Dr. [redacted], MB, [redacted] Kingdom.

Centre details:
Multi-centre study conducted at 14 centres (Canada: 4; United kingdom: 10)

Publication references:
To be decided.

| Study period details : | Phase of development: |
|---|---|
| First patient included 06 November 2006<br>Last patient attended last visit 11 July 2007 | Phase II |

Objectives/hypothesis, if applicable:
To compare the efficacy and safety of two different dose combinations of LEO 19123 cream (calcipotriol and LEO 80122) with LEO 19123 cream vehicle for 3 weeks in the treatment of patients with hand eczema.

Study methodology:
An international, multi-centre, prospective, randomised, double-blind, 3 arm, vehicle-controlled, parallel group, 3-week phase II clinical study in patients with hand eczema. Patients were treated on the hands only (back of the hands, palms, fingers and wrists) once daily in the evening for 3 weeks with either a) LEO 19123 cream (calcipotriol 50 mcg/g and LEO 80122 0.6 mg/g; henceforth referred to as LEO 19123 50/0.6) or b) LEO 19123 cream (calcipotriol 15 mcg/g and LEO 80122 0.2 mg/g; henceforth referred to as LEO 19123 15/0.2) or c) LEO 19123 cream vehicle (henceforth referred to as LEO 19123 vehicle). Vinyl gloves were used to apply other topical medication on areas other than the hands. Following a screening visit (Visit 0) a wash-out period of up to 28 days was completed if the patient was treated, or had recently been treated for hand eczema or used other relevant medication, as defined in the exclusion criteria. Study visits were performed at baseline

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(Visit 1) when the patch test results were available and randomisation occurred, then after 3 (Visit 2), 7 (Visit 3), 14 (Visit 4) and 21 (Visit 5) days. A follow up visit (Visit 6) at day 35 was performed for those patients who completed the 3 week treatment period and for those patients who withdrew prematurely due to a treatment-related adverse event (possible, probable or not assessable). During the follow up phase, no treatment for hand eczema was allowed except for emollient.

Efficacy assessments including the Investigator's global assessment of disease severity (IGA), Investigator's clinical assessments (erythema, induration/papulation, vesicles, fissuring, scaling and oedema) for the Hand Eczema Severity Index (HECSI), the Patient's overall assessment of disease severity and the Patient's assessment of pruritus were performed at baseline and all subsequent visits (1 to 6). Blood samples for haematology and clinical chemistry assessment were taken at baseline, at Days 7, 21, early withdrawal (Visits 2 or 4) and Follow-up (Visits 1, 3, 5 and 6) and adverse events were recorded at Days 3, 7, 14, 21 and Follow-up (Visits 2 to 6. For patients in the United Kingdom Total IgE was measured at baseline (Visit 1). Cosmetic acceptability was assessed by the patient after 7 days of treatment (Visit 3).

Number of patients enrolled :

A total of 75 patients were planned (25 patients in each of the three treatment groups). A total of 91 were enrolled and 81 were randomised: 26 to LEO 19123 50/0.6, 32 to LEO 19123 15/0.2 and 23 to LEO 19123 vehicle.

Diagnosis and main criteria for patient selection:

Caucasian male hospital out patients or patients attending the private practise of a dermatologist, aged 18 years or over, with a clinical diagnosis of hand eczema with or without atopic etiology/background and with an IGA of at least mild at baseline (Visit 1). Informed consent given. Exclusions were current diagnosis of exfoliative dermatitis, concurrent skin diseases on the hands, significant clinical infection (impetiginsed hand eczema) on the hands requiring antibiotic treatment, positive patch test, history of cancer (except basal cell carcinoma), systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azothioprine) or corticosteroids, PUVA or UVB on the hands within 4 weeks of randomisation, topical treatment with immunomodulators (pimecrolimus, tacrolimus) within

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2 weeks of randomisation or other topical therapy on the hands except for emollients within 1 week of randomisation. Use of drug/nondrug treatment on the hands (other than study treatment and emollient) during the study was also excluded.

Investigational product, dose, method of administration, lot numbers:

LEO 19123 50/0.6: calcipotriol 50 mcg/g and LEO 80122 0.6 mg/g. Lot numbers: 06 244 6101, 06 313 6101 and 07 110 6101

LEO 19123 15/0.2: calcipotriol 15 mcg/g and LEO 80122 0.2 mg/g. Lot numbers: 06 243 6101, 06 312 6101 and 07 103 6101

Products were applied topically to affected areas on the hands (back of the hands, palms, fingers and wrists) once daily in the evening before bedtime to a maximum of 30 g per week.

Reference product, dose, method of administration, lot numbers:

LEO 19123 vehicle: Lot numbers: 06 238 6101 and 06 310 6101

The reference product was applied topically to affected areas on the hands (back of the hands, palms, fingers and wrists) once daily in the evening before bedtime to a maximum of 30 g per week.

Duration of treatment:

Up to 3 weeks

Criteria for evaluation

Efficacy :

Primary Response Criterion:

IGA on the hands at the end of treatment (EOT).

Secondary Response Criteria:

The percentage change in the HECSI on the hands from baseline (randomisation) to EOT.

Patient's assessment of pruritus on the hands at EOT.

Patient's overall assessment of disease severity at EOT.

Patients who achieved 'controlled disease' ('clear' or 'almost clear' for patients with at least moderate disease at baseline; 'clear' for patients with mild disease at baseline) according to IGA at EOT.

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Safety:

Any reported adverse events (AEs) or adverse drug reactions (ADRs). Reasons for withdrawal from the study. Changes in haematology and blood chemistry (absolute change from baseline to each visit and relative change by categorising values as low, normal or high).

Statistical methodology:

The primary response criterion was analysed for the full analysis set (primary) and the per protocol set. The IGA on the hands at EOT was evaluated for an effect of treatment using the proportional odds model with concentrations 0, 1, 3 as a covariate and IGA at baseline and centre as factors. For each dose combination of LEO 19123 cream and LEO 19123 cream vehicle, the cumulative odds ratio, its 97.5% confidence interval (CI), and a P-value were estimated in a proportional odds model with treatment group, IGA at baseline, and centre as factors. A CI of 97.5% was chosen to account for multiplicity using the Bonferroni method. For the secondary response criteria the Hochberg correction was used to account for multiplicity and 95% CIs were estimated for descriptive purposes only. The percentage change in HECSI from baseline to EOT was analysed using the Kruskal Wallis test, the patient's overall assessment of disease severity and the patient's assessment of pruritus were analysed using the proportional odds model with concentrations 0, 1, 3 as covariate and the patients baseline assessment and centre as factors. 'Controlled disease' was analysed in a logistic regression model with concentrations 0, 1, 3 as covariate and centre as a factor.

Summary – Conclusions

Efficacy results:

The primary response criterion was IGA at EOT. At baseline, 28.4% of patients had mild, 53.1% moderate, 16.0% severe and 2.5% had very severe disease according to the IGA. At EOT few patients achieved clear/almost clear (2 in the LEO 19123 vehicle group, 3 in the LEO 19123 15/0.2 group and 4 in the LEO 19123 50/0.6 group) and the majority in each treatment group were in the mild/moderate aggregated category with 69.5%, 68.8% and 65.4% for the LEO 19123 vehicle group, LEO 19123 15/0.2 group and LEO 19123 50/0.6 groups, respectively. At EOT the difference between the treatments was not statistically significant (odds of improvement per unit increase in concentration OR 1.04; 95% CI 0.68 to 1.58; P=0.87). Furthermore the pair-wise comparisons between each of the active treatments and the LEO 19123 vehicle were not statistically significant (OR 0.87; 97.5% CI

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0.22 to 3.49; P=0.82 for LEO 19123 15/0.2 vs vehicle and OR 1.06; 97.5% CI 0.24 to 4.68; P=0.93 for LEO 19123 50/0.6 vs vehicle). The per protocol analyses confirmed these results.

There were four secondary efficacy response criteria (HECSI, patient's overall assessment of disease severity, patient's assessment of pruritus and patients with 'controlled disease'). None of the secondary efficacy response criteria demonstrated statistical significance or a tendency to efficacy for either of the active treatments.

Safety results:

The proportion of patients with AEs did not differ significantly across the treatment groups (P=0.98). The most common AEs in the LEO 19123 vehicle group occurred in the SOC Investigations, Metabolism and nutritional disorders and skin and subcutaneous tissue disorders. In both the active groups the most common AEs were in the SOC Skin and subcutaneous tissue disorders but for LEO 19123 15/0.2 AEs occurred with the same frequency also in the SOC Nervous system disorders.

In all three groups 'eczema' was one of the most common preferred terms occurring in 2 (8.7%) patients in the LEO 19123 vehicle group, 3 (9.7%) patients in the LEO 19123 15/0.2 group and 4 (15.4%) patients in the LEO 19123 50/0.6 group. The most common ADRs (occurring in more than one patient) were 'eczema', 'hypercholesterolaemia' and 'hyperglycaemia'. The incidence of 'eczema' appeared to increase with increasing dose but the incidences of both 'hypercholesterolaemia' and 'hyperglycaemia' in the active treatment groups were similar to vehicle. The number of patients that withdrew due to AEs were few and similar in all groups (three in the LEO 19123 vehicle group, three in the LEO 19123 15/0.2 group and four in the LEO 19123 50/0.6 group) and most common AEs that lead to discontinuation were eczema related. No clinically relevant changes in laboratory parameters over time in the active treatment groups relative to vehicle treated group were observed. There were no deaths and one SAE (head injury) unrelated to study treatment in the LEO 19123 50/0.6 group.

Conclusion:

Neither of the active treatments (LEO 19123 15/0.2 nor LEO 19123 50/0.6) was more effective than the LEO 19123 vehicle in the treatment of hand eczema over 3 weeks. No

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| statistically significant difference (or trend towards a difference) in efficacy was seen between the two active LEO 19123 treatments compared to the vehicle. Proof-of-concept was not demonstrated in this GCP study. | | |
| Report date:<br>18 MAR-2008 | | |

## 3.1 SCHEDULE/CHART OF STUDY PROCEDURES

| **Visit** | **0 Screening** [a)] | **1 Randomi-sation (baseline)** | **2** | **3** | **4** | **5 or Early withdrawal** | **6 Follow-up** [b)] |
|---|---|---|---|---|---|---|---|
| **Day** | **-28 to -2** | **0** | **3** | **7** | **14** | **21** | **35** |
| **Visit window (days)** | | | **±1** | **±1** | **±2** | **±2** | **±2** |
| Informed consent | x | | | | | | |
| Patient demographics (incl. height and weight) | x | | | | | | |
| In/exclusion criteria | x | x | | | | | |
| Concomitant treatment | x | x | x | x | x | x | x |
| Medical history | x | x | | | | | |
| Patch Test [c)] | x | | | | | | |
| Randomisation | | x | | | | | |
| Adverse event(s) | | | x | x | x | x | x |
| Haematology, APTT | | x | | x | | x | x |
| Blood chemistry | | x | | x | | x | x |
| Clinical photographs [d)] | | x | x | x | x | x | x |
| Investigator's global assessment | | x | x | x | x | x | x |
| Investigator's clinical assess-ments for HECSI | | x | x | x | x | x | x |
| Patient's overall assessment | | x | x | x | x | x | x |
| Patient's assessment of pruritus | | x | x | x | x | x | x |
| Patient's cosmetic acceptability | | | | x | | | |
| Dispensing of investigational product | | x | | x | x | | |
| Dispensing of other treatment [e)] | x | x | | x | x | x | |
| Compliance | | x | x | x | x | x | |
| Return of used/unused investigational product | | | | x | x | x | |
| End of Trial Form | | x [f)] | | | | x [f)] | x |

a) The screening period was defined as the time between Visit 0 and Visit 1. The screening period included any washout period. This period varied between 2 and 28 days depending on whether the patient was using a treatment for hand eczema.
b) Follow-up (FU) Visit was applicable for all randomised patients who had completed the 3-weeks treatment. If a patient was prematurely withdrawn from the trial due to an adverse event classified as possibly or probably related to the investigational product or not assessable in relation to the investigational product, a follow-up visit was to be completed.
c) Patch test of LEO 19123 cream vehicle. See section. 11.7.5.2.
d) Clinical photographs were obtained from one designated site.
e) Other trial medication: Diprobase® cream and Unguentum M® cream. This was to be dispensed on an individual basis per patient as needed.
f) If a patient was not randomised or when a patient was withdrawn/completing the trial, the End of Trial Form was to be completed.

**Clinical Study Report LEO19123-C22 EudraCT no. 2006-002686-39 LEO19123 Cream in the Treatment of Hand Eczema 2007-12-21**

**eDoc LEO RD 00111967**
**Version Number: 1.0**

## Approvals

| Name | Type | Reason for signature | Date for signature |
|---|---|---|---|
| [redacted] | Approved | [redacted] Biostatistics Department | 02-Apr-2008 10:36:34 AM |
| [redacted] | Approved | [redacted], International Clinical Development | 03-Apr-2008 10:55:50 AM |
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