# Clinical Study Report Synopsis

# Effect of Calcipotriol Plus Hydrocortisone Ointment on the HPA Axis and Calcium Metabolism in Patients with Psoriasis Vulgaris on the Face and on the Intertriginous Areas

**A phase 2 study evaluating the safety and efficacy of calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g ointment applied once daily in the treatment of psoriasis vulgaris on the face and on the intertriginous areas**

An international, multi-centre, prospective, open, non-controlled, 8-week clinical study

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

**LEO 80190-O23**
**Report Date 29-OCT-2010**
**EudraCT-No. 2007-005501-22**

# 1 CLINICAL STUDY REPORT SYNOPSIS APPROVAL

## 1.1 APPROVAL STATEMENT

On behalf of LEO, only the Head of International Clinical Development, LEO and the Head of Biostatistics, LEO HQ are authorised to approve the Clinical Study Report Synopsis.

All LEO approvers will be identified on a signature page of the pdf-file of the final Clinical Study Report Synopsis when the last LEO approval is obtained. The time and date of their e-signatures are likewise presented on the approval page.

The following persons have approved this Clinical Study Report Synopsis using electronic signatures:

[redacted] Biostatistics, LEO HQ

[redacted] International Clinical Development, LEO [redacted], Clinical Development

## 1.2 APPROVAL STATEMENT INVESTIGATORS

On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report Synopsis. The International Co-ordinating Investigator approves the Clinical Study Report Synopsis by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this document.

The following person has approved this Clinical Study Report Synopsis

Dr. [redacted], Germany
International Co-ordinating Investigator

# 2 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>LEO 80190 Ointment | Volume: | |
| Name of Active Substance:<br>Calcipotriol plus hydrocortisone Ointment | Page: | |

Title of study/protocol code number:

Effect of Calcipotriol Plus Hydrocortisone Ointment on the HPA Axis and Calcium Metabolism in Patients with Psoriasis Vulgaris on the Face and on the Intertriginous Areas.
LEO 80190-O23

International Co-ordinating Investigator:

Dr. [redacted], Germany

Trial sites:

Multicentre study conducted at 14 centres (Canada 5 centres, Germany 2 centres, United Kingdom 2 centres and the US 5 centres)

Publication (reference):

To be decided

| Studied period: | Phase of development: |
|---|---|
| First subject first visit: 16-JUN-2008<br>Last subject last visit: 03-DEC-2009 | II |

Objectives:

To evaluate the effect of once daily use of calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g ointment (hereafter referred to as LEO 80190 ointment) on the hypothalamic-pituitary-adrenal (HPA) axis and on calcium metabolism in subjects with psoriasis vulgaris on the face and on the intertriginous areas.

Methodology:

An international, multi-centre, prospective, open, non-controlled study with up to 8 weeks once daily topical application of LEO 80190 ointment in subjects with psoriasis vulgaris on the face and intertriginous areas.

Visits were as follows: a Screening Visit (SV) within 28 to 3 days before first drug administration at Day 0 (Visit 1), a washout phase of up to 30 days (if required), a Baseline Visit (BV) within 7 to 3 days prior to Day 0 (Visit 1), a 4 or 8 week with visits on Days 0, 14, 28, 42, and 56 (Visits 1, 2, 3, 4, and 5). An adrenocorticotropic hormone (ACTH) challenge test for assessment of HPA axis function was performed at 8 a.m. at BV and after 4 and 8 weeks treatment at Days 28 and 56 (Visits 3 and 5). If HPA axis suppression was noted at Visits 3 or 5 a follow-up visit (FU2) was conducted 28 days later and the ACTH challenge test was repeated. If an adverse event (AE) classified as possibly/probably related or not assessable in relation to the study medication was ongoing, or an albumin corrected serum calcium value was outside the reference range, at the subject's last on-treatment visit, FU1 took

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place 14 days after that visit. Starting on Day 0 (Visit 1) LEO 80190 ointment was applied to all lesions on the face and intertriginous areas. LEO 80190 ointment was to be applied once daily every day expect in the 24-hour period prior to the ACTH challenge test at Days 28 and 56 (Visits 3 and 5). Subjects who had achieved clear according to the investigator's global assessment of disease severity (IGA) of the face and of the intertriginous areas at Day 28 (Visit 3) left the study; subjects who had psoriasis on the face and/or on the intertriginous areas after 4 weeks treatment continued once daily treatment for another 4 weeks. A physical examination was conducted at the SV and BV, vital signs and ECG were conducted at the BV. At BV and Days 28 and 56 (Visits 3 and 5) routine blood and urine laboratory tests were performed. Serum calcium and albumin were assessed pre-treatment (SV and BV) and during treatment on Days 14, 28, 42 and 56 (Visits 2, 3, 4 and 5). Adverse events were recorded at all visits except SV. Psoriasis lesions were assessed on the face and intertriginous areas separately at all visits except FU1 and FU2.

Number of subjects enrolled:

A total of 75 subjects were enrolled and screened and 33 were eligible and received treatment.

Diagnosis and main criteria for eligibility:

Subjects of either sex, any race or ethnicity, aged 18 years or above with a clinical diagnosis of psoriasis vulgaris involving the face and the intertriginous areas amenable to topical treatment with a maximum of 100 g of study medication per week and clinical signs of, or earlier diagnosed with, psoriasis vulgaris on the trunk and/or the limbs. Disease severity of the face and of the intertriginous areas graded as at least moderate according to the IGA of the face and the intertriginous areas with an extent of the psoriatic involvement on the face of at least 5 $cm^2$ and on the face and intertriginous areas of at least 30 $cm^2$ (the sum of all facial and intertriginous lesions). Normal HPA axis function and albumin corrected serum calcium within the reference range at BV. Informed consent given.

The following were not permitted during the study or within the specified time of study start. Systemic treatment with all other therapies than biologicals, with a potential effect on psoriasis vulgaris (e.g., vitamin D analogues, retinoids) except stable treatment (same dose for at least 4 weeks) with methotrexate or fumaric acid within 2 weeks prior to Visit 1. Initiation of or increases in dose of methotrexate or fumaric acid within 4 weeks prior to Visit 1 or during the study was not allowed. (Protocol Amendment No: 003). Treatment immunosuppressants was not permitted before the protocol amendment. Systemic treatment with corticosteroids (including inhaled) within 12 weeks prior to Visit 1. Systemic use of biological treatments, whether marketed or not, directed against or with a potential effect on psoriasis vulgaris (e.g., alefacept, efalizumab, etanercept, infliximab, adalimumab) within 12 weeks prior to Visit 1. Psoralen plus ultraviolet A therapy or Grenz ray therapy within 4

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weeks prior to Visit 1. Ultraviolet B therapy within 2 weeks prior to Visit 1. Topical treatment of the face, trunk/limbs or the scalp with topical World Health Organisation (WHO )group 2, 3 and 4 corticosteroids within 4 weeks prior to Visit 1. Topical treatment of the face, trunk/limbs or the scalp with topical WHO group 1 corticosteroids within 2 weeks prior to Visit 1. Any topical treatment of the face or the intertriginous areas (except for emollients) within 2 weeks prior to Visit 1.

Subjects with erythrodermic, exfoliative, guttate or pustular psoriasis, other skin diseases, irregular sleep schedules, signs or symptoms of Cushing's disease or Addison's disease, known or suspected to have endocrine disorder that may affect the ACTH challenge test, severe renal insufficiency, severe hepatic disorders or disorders of calcium metabolism associated with hypercalcaemia were excluded.

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

LEO 80190 ointment: Calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g ointment

Lot numbers: 0731661, 0821761, 0822161

Locobase® fatty cream used as an emollient.

Tetracosactid/cosyntropin used only as test product for the ACTH challenge test.

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

Not applicable.

Duration of treatment:

Up to 8 weeks.

Criteria for evaluation

Safety:

Primary endpoints:

The adrenal response to the ACTH challenge test defined as the serum cortisol concentration obtained after 30 and 60 minutes at Week 4 and Week 8 and the Change in albumin corrected serum calcium from baseline to Weeks 4 and 8 and end of treatment.

Secondary end points were:

Adrenal response to the ACTH challenge test defined as the serum cortisol concentration obtained after 30 and 60 minutes at Week 4 and Week 8.

Serum cortisol concentration after 30 and 60 minutes at Week 4 and Week 8.

Change in albumin corrected serum calcium from baseline to Weeks 2 and 6.

Albumin corrected serum calcium at Weeks 2, 4, 6 and 8 and end of treatment.

Albumin corrected serum calcium values above the upper limit of the reference range at Weeks 2, 4, 6 and 8 and end of treatment.

Any reported treatment emergent AEs or adverse drug reactions (ADRs).

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Any reported treatment emergent AEs or ADRs on the face or the intertriginous areas.

Reasons for withdrawal from the study.

Efficacy :

Patients with "Controlled disease" ("Clear" or "Almost clear") according to the IGA of the face at Week 4, Week 8 and end of treatment.

Patients with "Controlled disease" ("Clear" or "Almost clear") according to the IGA of the intertriginous areas at Week 4, Week 8 and end of treatment.

IGA of the face and of the intertriginous areas at each visit and end of treatment.

Statistical methodology:

The analysis of the ACTH stimulation test was based on the per protocol analysis set (n=30), adverse event and laboratory data were analysed using the safety analysis set and the efficacy analysis was based on the full analysis set. All subjects (n=33) were included in the safety and efficacy analysis sets. The number of subjects with serum cortisol concentration ≤18 mcg/dL after 30 minutes and 60 minutes post injection and after each of 30 minutes and 60 minutes post injection were to be tabulated at Week 4 (Visit 3) and Week 8 (Visit 5). Serum albumin corrected calcium values were summarised for each visit and the mean change from baseline (Visit 1) to each visit and the end of treatment was estimated. Serum albumin corrected calcium values were categorised as 'low', 'normal' or 'high' with respect to reference ranges and shift tables of values at each visit versus the baseline category were produced. Summary statistics were also presented for serum cortisol after each of 30 and 60 minutes post injection. For treatment-emergent adverse events the number of patients experiencing each adverse event (preferred term) and the percentage of patients with adverse events was tabulated. Laboratory values were listed, flagged for values outside the reference ranges and summarised by visit where appropriate for observed values and changes from baseline (BV). The frequency of patients who achieved 'controlled disease' according to the IGA was calculated for the face and the intertriginous areas separately.

Summary – Conclusions

Safety results:

There was no evidence of HPA suppression in this study. The serum cortisol concentrations obtained after 30 and 60 minutes post injection, at Week 4 and Week 8, were always >18 mcg/dL, except for one subject who had a serum cortisol concentration of 13.3 mcg/dL obtained after 30 minutes post injection at Week 4. The time zero sample for this subject was above the upper limit of the normal unstimulated range and the 60 minute value was high as expected after stimulation. The sponsor and investigator believe that the time zero and 30 minute samples had been switched in error. At baseline and Week 8, this subject had normal cortisol at time zero and high values as expected at 30 and 60 minutes post the

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ACTH test. The mean serum cortisol concentrations 30 minutes after the ACTH stimulation test were: 26.40 mcg/dL (baseline), 25.29 mcg/dL (Week 4) and 25.93 mcg/dL (Week 8) and at 60 minutes after the test were: 29.69 mcg/dL (baseline), 28.81 mcg/dL (Week 4) and 28.82 mcg/dL (Week 8).

The mean changes in albumin corrected serum calcium from baseline (value 2.215 mmol/L) were: 0.018 mmol/L (95% CI −0.016 to 0.052) at Week 2, 0.002 mmol/L (95% CI −0.026 to 0.029) at Week 4, −0.013 (95% CI −0.045 to 0.020) at Week 6, −0.045 mmol/L, (95% CI −0.083 to −0.007) at Week 8 and −0.033 mmol/L (95% CI −0.066 to 0.000) at the end of treatment . There were no clinically relevant shifts for albumin corrected serum calcium for any subject. No clinically relevant effect on calcium metabolism was observed.

In total, 15 (45.5%) patients reported 31 adverse events. The most common adverse events were in the SOCs 'Infections and Infestations' and 'Nervous system Disorders' reported with equal incidence: 5 (15.2%) patients. The most common adverse events by preferred term were headache (4 patients), nasopharyngitis (3 patients) and nausea and back pain (2 patients each). All the events were mild or moderate in intensity. Adverse drug reactions were reported for 4 (12.1%) subjects. Headache (2 patients) was the only adverse drug reaction reported by more than 1 patient. One lesional/perilesional adverse event on the face was reported (pruritus). Three lesional/perilesional adverse events on the intertriginous areas were reported by one subject: Application site burning; Application site pruritus and Groin pain. There were no changes in any of the routine laboratory assessments (haematology, clinical chemistry or urine parameters) reported as adverse events. There were no deaths or other serious adverse events reported and no patients withdrew due to adverse events.

Efficacy results:

At end of treatment, the percentage of patients with 'controlled disease' according to the IGA on the face was 69.7% and on the intertriginous areas was 69.7%. At Week 4 the results were 63.6% for the face and 60.6% for the intertriginous areas.

Conclusion: In subjects with psoriasis vulgaris involving the face and intertriginous areas, application of LEO 80190 ointment had no effect on the HPA axis. Furthermore, there were no changes of clinical concern regarding the effect on calcium metabolism. The adverse event profile of LEO 80190 ointment was similar to that seen in other studies in psoriasis of the face with or without the intertriginous areas.

Date of report: 29-OCT-2010

## 2.1 SCHEDULE/CHART OF STUDY PROCEDURES

| Visit | SV[a)] | Baseline[c)] | 1 | 2 | 3 | 4 | 5 | FU1[d)] | FU2 |
|---|---|---|---|---|---|---|---|---|---|
| **Day** | **Within –28 to -3** | **Within –7 to –3** | **0** | **14 ± 2** | **28 ± 2** | **42 ± 2** | **56 ± 2** | **+14 ± 2** | **+28 ± 2** |
| Informed consent | X[b)] | | | | | | | | |
| Demographics | X | | | | | | | | |
| Duration of psoriasis vulgaris | X | | | | | | | | |
| Physical examination | X | X | | | | | | | |
| Vital signs (blood pressure, pulse) and ECG | | X | | | | | | | |
| Biochemistry (blood and urine) and Haematology | | X | | | X | | X | | |
| Serology (Hepatitis B/C, HIV) | X | | | | | | | | |
| Drugs of abuse/alcohol screen[e)] | X | X | | | | | | | |
| ACTH challenge test: tetracosactid/cosyntropin injection i.v. and blood sampling at T=0, 30 minutes and 60 minutes | | X 8 a.m. | | | X 8 a.m. | | X 8 a.m. | | X[f)] 8 a.m. |
| Serum calcium and albumin | X | X | | X | X | X | X | X[g)] | |
| Serum pregnancy test[h)] | X | | | | X | | X | | |
| Urine pregnancy test[i)] | | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | |
| Adverse event | | X | X | X | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X | X | X | |
| Concurrent diagnoses | X | | | | | | | | |
| Investigator's assessment of extent of psoriasis vulgaris | | X | | | | | | | |
| Investigator's global assessment of disease severity | X | X | X | X | X | X | X | | |
| Dispensing of study medication | | | X | X | X | X | | | |
| Collection of study medication | | | | X | X | X | X | | |
| Compliance | | | | X | X | X | X | | |

a) Screening Visit (SV), prior to Visit 1, a washout period (up to 4 weeks) was completed if the subject was treated or had recently been treated with anti-psoriatic treatments or other relevant medication as defined by the exclusion criteria.

b) If the subject entered washout period, an informed consent form was completed beforehand.

c) Within 1 week prior to Visit 1, a baseline visit was performed. In order to have the results of the HPA axis function test available in due time, the Baseline Visit was performed at least 3 days prior to Visit 1.

d) Follow-up (FU1) visit/contact: only applicable if an adverse event (serious or non-serious) classified as possibly or probably related to the study medication or not assessable in relation to the study medication was present at the subject's last on-treatment visit. This follow-up was performed 14 ±2 days after the subject's last on-treatment visit or until final outcome of the adverse event is determined, whichever came first.

e) The test could be performed at any time during the study period, if the investigator suspected that an abuse had occurred.

f) If laboratory results suggested HPA axis suppression at Visit 3 or Visit 5, a follow-up test was performed 28 ±2 days later at Visit FU2.

g) If laboratory results suggested albumin corrected serum calcium outside reference range at the last on-treatment visit, a follow-up test was performed.

h) If female of childbearing potential, a serum pregnancy test was performed at the Screening Visit, Visit 3 and Visit 5.

i) If female of childbearing potential, a urine pregnancy test was performed at the Baseline Visit.

# LEO 80190-O23 Clinical Study Report Synopsis LEO 80190-O23 Clinical Study Report Synopsis - English

## ELECTRONIC SIGNATURES

*Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.*

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'GMT'Z) |
|---|---|---|
| [redacted] | [redacted], International Clinical Development Approval | 03-nov-2010 16:56 GMT+01 |
| [redacted] | [redacted] Biostatistics Approval | 04-nov-2010 14:54 GMT+01 |