Clinical Study Report Synopsis

A psoriasis plaque test study with LEO 90100 cutaneous spray, ointment, in psoriasis vulgaris

A phase 2a exploratory study evaluating LEO 90100 cutaneous spray, ointment compared to Daivobet® ointment, LEO 90100 cutaneous spray, ointment, vehicle with betamethasone dipropionate, and LEO 90100 cutaneous spray, ointment, vehicle in the treatment of psoriasis vulgaris.

A single centre, investigator-blinded, active- and vehicle- controlled, 4 weeks, repeated dose study with intra-individual comparison.

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

Trial ID: LEO 90100-01
EudraCT Number: 2011-000153-23

15-NOV-2011
CLINICAL STUDY REPORT SYNOPSIS APPROVAL

APPROVAL STATEMENT
On behalf of LEO, only the Head of International Clinical Development and the Head of Biostatistics and Data management, 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:

Biostatistics and Data Management, LEO HQ

International Clinical Development

APPROVAL STATEMENT INVESTIGATORS
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 report.

The following person has approved this Clinical Study Report Synopsis

CPCAD, Nice, France
International Co-ordinating Investigator
### SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>LEO Pharma A/S</th>
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<td>Name of Finished Product:</td>
<td>Individual Trial Table Referring to Part of the Dossier</td>
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<td>Name of Active Ingredient:</td>
<td>LEO 90100</td>
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#### Title of trial:
A psoriasis plaque test study with LEO 90100 cutaneous spray, ointment, in psoriasis vulgaris

#### Investigator:
Dr. [Redacted]

#### Trial centre:
Single centre, investigator-blinded, active- and vehicle-controlled, 4 weeks, repeated dose study, with intra-individual comparison.

#### Publication (reference):
Not applicable

#### Trial period (years):
2 months

#### Date of first enrolment:
12-MAY-2011

#### Date of last completed:
20-JUN-2011

#### Objectives:
The primary objective of the study was to evaluate the anti-psoriatic effect of LEO 90100 cutaneous spray, ointment compared to Daivobet® ointment, LEO 90100 cutaneous spray, ointment, vehicle with betamethasone dipropionate and LEO 90100 cutaneous spray, ointment, vehicle.

The secondary objective was to obtain information on adverse events for all investigational products.

#### Methodology:
A single centre, investigator-blinded, active- and vehicle-controlled, 4 weeks, repeated dose study, with intra-individual comparison.

The study consisted of a screening visit, a wash-out period if needed, a treatment period of 29 days and, if applicable, a follow-up visit. Within 21 days before treatment a screening visit for study eligibility of the subjects took place. During the treatment phase, three (3) investigational products (LEO 90100 cutaneous spray, ointment, LEO 90100 cutaneous spray, ointment, vehicle with betamethasone dipropionate and LEO 90100 cutaneous spray, ointment, vehicle) and the reference product (Daivobet® ointment) were applied once daily 6 days a week (except Sundays) for 4 weeks. The subjects received study medication on four (4) test sites of 5 cm² selected on predetermined psoriasis lesions (target plaques), delimited with a disposable circular device and mapped on a drawn figure. Twice a week during the treatment phase, clinical assessments were performed (Days 1, 4, 8, 11, 15, 18, 22, 25 and 29). Ultrasound measurements of skin thickness were performed at Days 1 (baseline), 8, 15, 22 and 29 (end of treatment phase). During the study, local and systemic adverse events were reported on an ongoing basis. If an adverse event (serious or non-serious), classified as possible or probably related to the study medication or not assessable in relation to the trial medication, was ongoing at the subject’s last on-treatment visit, a follow-up visit/contact was to take place 14 (+2) days after that visit.

#### Number of subjects (planned and analysed):
24 subjects were enrolled and 24 subjects were randomised (16 males and 8 females with mean age of 50 years).

#### Diagnosis and main criteria for inclusion:
**Main criteria for inclusion:**
1. Following verbal and written information about the trial, the subject had to provide signed and dated informed consent before any study related activities were carried out.
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Name of Finished Product: Vohune:

Name of Active Ingredient: LEO 90100

2. Age 18 years or above
3. Either sex
4. All skin types
5. Subjects with a diagnosis of psoriasis vulgaris with lesions located on arms, legs and/or trunk. The lesions had to have a total size suitable for application of 4 different products.
6. Subjects with, in the opinion of the investigator, stable psoriasis based on Total Plaque Score evaluated at screening visit and at visit 2 (Baseline)
7. Subjects with psoriasis lesions (plaques) assessed by a Total Clinical Score (sum of scores of erythema, scaling and infiltration) of 4 to 9 inclusive but each individual item ≥ 1
8. Subjects willing and able to follow all the study procedures and complete the whole study
9. Subjects affiliated to a social security system
10. Female subjects of childbearing potential using a reliable method of contraception for at least 1 month before the study start and during the course of the study (e.g., oral contraceptive pill, intrauterine device, contraceptive patches, implantable contraception, condoms) or females of non childbearing potential (i.e. postmenopausal (absence of menstrual bleeding for 2 years), hysterectomy, bilateral ovariectomy or tubal section/ligation)
11. Female with a negative urine pregnancy test (at screening visit).

Main criteria for exclusion:
1. Females who were pregnant, of child-bearing potential and who wished to become pregnant during the study, or who were breast feeding.
2. Systemic treatment with biological therapies (marketed or not marketed) with a possible effect on psoriasis vulgaris within 4 weeks (etanercept), 2 months (adalimumab, alefacept, infliximab), 4 months (ustekinumab) or 4 weeks/5 half-lives (which-ever was longer) for experimental biological products prior to randomisation and during the study.
3. Systemic treatments with all other therapies than biologicals, with a potential effect on psoriasis vulgaris (e.g., corticosteroids, retinoids, immunosuppressants) within the 4-week period prior to randomisation and during the study.
4. Use of phototherapy within the following time periods prior to randomisation and during the study:
   - PUVA or Grenz ray therapy (4 weeks)
   - UVB (2 weeks).
5. Subjects using one of the following topical drugs within 4 weeks prior to randomisation and during the study:
   - Potent or very potent (WHO group III-IV) corticosteroids.
6. Subjects using one of the following topical drugs for the treatment of psoriasis within 2 weeks prior to randomisation and during the study:
   - WHO group I-II corticosteroids (except if used for treatment of scalp and/or facial psoriasis)
   - Topical retinoids
   - Vitamin D analogues
   - Topical immunomodulators (e.g. calcineurin inhibitors)
   - Anthracen derivatives
   - Tar
   - Salicylic acid.
7. Subjects who had used emollients on the target plaques within one week before randomisation or during the study.
8. Initiation of, or expected changes in concomitant medication that could affect psoriasis vulgaris (e.g., beta blockers, antimalaria drugs, lithium and ACE inhibitors) within 2 weeks prior to randomisation or during the study.
9. Subjects with current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
10. Subjects with known/suspected disorders of calcium metabolism associated with hypercalcaemia within the last 10 years, based on medical history.
**Name of Sponsor/Company:** LEO Pharma A/S

**Name of Finished Product:** LEO 90100

**Name of Active Ingredient:** LEO 90100

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1. Subjects with any of the following conditions present on the test area: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections and atrophic skin.

2. Subjects with skin manifestations in relation to syphilis or tuberculosis, rosacea, perioral dermatitis, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, acne rosacea, ulcers and wounds within the plaque test areas.

3. History of any severe disease or serious current condition (based on subject interview and/or results of screening physical examination) which, in the opinion of the Investigator, would put the subject at risk by participating in the study or would interfere significantly with the evaluation of study results or the study course (e.g. cancer, severe cardiopathy, severe renal insufficiency, severe hepatic insufficiency).

4. Subjects who had received treatment with any non-marketed drug substance (i.e., an agent which had not yet been made available for clinical use following registration) within the 4 week period prior to randomisation or longer, if the class of the substance required a longer washout as defined above (e.g., biological treatments).

5. Subjects with current participation in any other interventional clinical trial, based on interview of the subject.

6. Subjects with known or suspected hypersensitivity to component(s) of the investigational products.

7. Subjects with any concomitant medical or dermatological disorder(s) which could preclude accurate evaluation of the psoriasis.

8. Subjects foreseeing an intensive solar exposure during the study (UV radiation, etc.) or having been exposed within two weeks preceding the screening visit.

9. Subjects impossible to contact in case of emergency.

10. Subjects who were known or, in the opinion of the investigator, were unlikely to comply with the Clinical Study Protocol (e.g. alcoholism, drug dependency or psychotic state).

11. Subjects who were in an exclusion period in the National Biomedical Research Register of the French Ministry of Health at randomisation.

12. Subjects under guardianship, hospitalized in a public or private institution, for a reason other than the research or subject deprived of freedom.

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**Test product, dose and mode of administration, batch number:**

1. LEO 90100 cutaneous spray, ointment, lot number 110647101 / expiry date 01-2012
2. LEO 90100 cutaneous spray, ointment, vehicle with betamethasone dipropionate, lot number 110637101 / expiry date 01-2012
3. LEO 90100 cutaneous spray, ointment, vehicle, lot number 110627101 / expiry date 12-2011

**Route of administration:** Topical. Dosage: 50 mg spray / 5 cm² diameter site

**Duration of treatment:** The treatment phase was 4 weeks (24 applications)

**Reference therapy, dose and mode of administration, batch number:**

Daiubat® ointment, pack lot number EE1965 / expiry date 06-2012

**Route of administration:** Topical. Dosage: 50 µl / 5 cm² diameter site

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**Criteria for evaluation:**

**Efficacy:**

The primary response criterion was the absolute change in Total Clinical Score (TCS) of clinical symptoms (sum of erythema, scaling and infiltration) at end of treatment compared to baseline.

The secondary response criteria were:

1. the absolute change in single clinical symptom score: erythema, scaling, infiltration at end of treatment and individual visits compared to baseline.
2. the change in TCS at individual visits compared to baseline.
3. the change in lesion thickness (total and echo-poor band) measured by ultrasound at end of treatment and individual visits compared to baseline.
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LEO Pharma A/S  

**Name of Finished Product:**
Vohume:  

**Name of Active Ingredient:**
- LEO 90100  

**Safety:**
Any reported adverse events (AEs) or adverse drug reactions (ADR).

**Statistical methods:**
The change in TCS from baseline to end of treatment was analysed using a two-way analysis of variance having subjects and treatments as factors. Treatment differences were tested as contrasts. Ninety five percent (95%) confidence interval of differences between treatments was calculated.

Due to the exploratory nature of the study, no correction to multiplicity was made in the primary analysis. A secondary analysis using Tukey’s honestly significant difference method for correcting P-values was produced in the two-way analysis of variance.

The difference between treatment profiles over time was tested in a repeated measurement model having subjects and treatments as factors and time points as the repeated factor.

The change in total skin thickness and echo-poor band thickness from baseline to end of treatment were analysed as described for change in TCS without any correction for multiplicity.

The absolute change in each component of the TCS (erythema, scaling and infiltration) from baseline to each assessment at Days 4, Day 8, Day 11, Day 15, Day 18, Day 22, Day 25 and Day 29 was presented for each treatment.

The change in skin thickness (echo-poor band and total) from baseline to Day 8, Day 15, Day 22 and Day 29 was presented for each treatment.

**SUMMARY - CONCLUSIONS**

**EFFICACY RESULTS:**
The mean change in TCS was -6.0, -1.9, -5.0 and -5.3 for LEO 90100 spray, ointment, LEO 90100 spray, ointment, vehicle, LEO 90100 spray, ointment, vehicle with betamethasone and Daivobet® ointment, respectively. The mean decrease in TCS was statistically significantly larger after treatment with LEO 90100 spray, ointment than with the other treatments.

The mean change in total skin thickness was -0.8, -0.2, -0.7 and -0.6 for LEO 90100 spray, ointment, LEO 90100 spray, ointment, vehicle with betamethasone and Daivobet® ointment, respectively. The mean decrease in total skin thickness was statistically significantly larger after treatment with LEO 90100 spray, ointment than with LEO 90100 spray, ointment, vehicle (p<0.001).

The mean change from baseline to end of treatment in echo-poor band thickness was -0.6, -0.1, -0.4 and -0.5 for LEO 90100 spray, ointment, LEO 90100 spray, ointment, vehicle, LEO 90100 spray, ointment, vehicle with betamethasone and Daivobet® ointment, respectively. The mean decrease in echo-poor band thickness was statistically significantly larger after treatment with LEO 90100 spray, ointment than with LEO 90100 spray, ointment, vehicle (p<0.001) and LEO 90100 spray, ointment, vehicle with betamethasone (p=0.037) and in limit of statistical significance as compared to Daivobet® ointment (p=0.052).

**SAFETY RESULTS:**
There were no ADRs, no withdrawals due to AEs or serious adverse events in the study.

**CONCLUSIONS:**
LEO 90100 spray, ointment was statistically significantly more effective with respect to TCS than:
- Daivobet®
- LEO 90100 spray, ointment, vehicle with betamethasone
- LEO 90100 spray, ointment, vehicle

The treatments were well tolerated.

**Date of the Report:** 15-NOV-2011
### SCHEDULE/CHART OF TRIAL PROCEDURES

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(1) Washout for maximum of 3 weeks, if applicable.
(2) The last application was performed on Day 27. Visits 3,4,6,7,9,10,12,13,15,16,18,19,21,22,24,25 were application only.
(3) For female subjects, a urine pregnancy test was performed at the screening visit.
(4) If the subject was not randomised, the End of Trial form should be completed.
(5) Photos of the test sites were taken for at least 2 subjects at Days 1 and 29.
(6) FU-follow-up visit/contact: If an adverse event (serious or non-serious) classified as possibly or probably related to study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit. Telephone contact or visit at the investigator’s discretion.
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.

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<th>Signed by</th>
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