Clinical Study Report Synopsis

LEO 90100 Compared with Calcipotriol plus Betamethasone Dipropionate Ointment, LEO 90100 Vehicle and Ointment Vehicle in Subjects with Psoriasis Vulgaris

A phase 2 study comparing treatment with LEO 90100 with calcipotriol plus betamethasone ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris.

A multi-centre, prospective, randomised, investigator blinded, 4-arm, parallel group, 4-week study in subjects with psoriasis vulgaris.
CLINICAL STUDY REPORT SYNOPSIS APPROVAL

APPROVAL STATEMENT
The following persons have approved this Clinical Study Report on behalf of LEO Pharma A/S using electronic signatures:

Biostatistics and Data Management
Medical Department

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:

International Co-ordinating Investigator
SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S

Name of Finished Product: LEO 90100, aerosol, foam

Name of Active Ingredient: Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)

Individual Trial Table
Referring to Part of the Dossier
Volume:
Page:

Name of Sponsor/Company: LEO Pharma A/S

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Title of trial:
A phase 2 study comparing treatment with LEO 90100 with calcipotriol plus betamethasone ointment, LEO 90100 vehicle and ointment vehicle in subjects with psoriasis vulgaris.

Investigators: The international co-ordinating investigator was, MD, University of California, San Francisco School of Medicine, 515 Spruce Street San Francisco, CA 94143, USA

Trial centre(s): The trial was conducted at 35 centres in the USA.

Publication (reference): None at the time of writing this report.

Trial period (years)
First subject enrolled: 10-May-2012
Last subject last visit/completed: 19-Sep-2012

Phase of development: II

Objectives:
The primary objective was to compare the efficacy of treatment with LEO 90100 with Calcipotriol plus betamethasone dipropionate (BDP) ointment for up to 4 weeks in subjects with psoriasis vulgaris. Secondary objectives were:
• To compare the safety of treatment with LEO 90100 with Calcipotriol plus BDP ointment for up to 4 weeks in subjects with psoriasis vulgaris.
• To compare the efficacy at week 1 of treatment with LEO 90100 with Calcipotriol plus BDP ointment in subjects with psoriasis vulgaris.

Methodology:
A multi-centre, prospective, randomised, investigator blinded, 4-arm, parallel group, 4-week trial in subjects with psoriasis vulgaris. Subjects with psoriasis vulgaris on the trunk and/or limbs of least mild severity according to the Investigators global assessment of disease severity (IGA) were enrolled. Eligible subjects were randomised in a 3:1:3:1 ratio to receive treatment with either:
• LEO 90100
• LEO 90100 vehicle
• Calcipotriol plus BDP ointment
• Ointment vehicle

The randomisation of subjects was according to their baseline disease severity (mild:at least moderate) as determined by the IGA. Prior to randomisation, a washout period (up to 4 weeks) was completed if the subject was treated, or had recently received, anti-psoriatic treatments, as defined in the exclusion criteria. Study
<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Individual Trial Table</th>
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<tbody>
<tr>
<td>LEO Pharma A/S</td>
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<td>Name of Finished Product:</td>
<td>Volume:</td>
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<tr>
<td>LEO 90100, aerosol, foam</td>
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<tr>
<td>Name of Active Ingredient:</td>
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<tr>
<td>Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)</td>
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</table>

Medication was applied to all psoriatic lesions on the trunk and/or limbs once daily for up to 4 weeks. Concurrent anti-psoriatic treatments were not allowed, except for emollients. Four study visits were performed during the treatment phase: Day 0 (Visit 1), after 1 week (Visit 2), after 2 weeks (Visit 3) and after 4 weeks (Visit 4). A safety follow up was scheduled, if required. Subjects classified as ‘clear’ at Visit 2 or 3 were allowed to stop treatment at the (sub)investigator’s discretion. Subjects remained in the trial and were to attend all scheduled visits. If their psoriasis reappeared subjects were advised to reinitiate the treatment without consulting the (sub)investigator.

Number of subjects (planned and analysed):
The plan was to enrol 400 subjects; 150 subjects in the active groups and 50 in the vehicle groups. A total of 376 subjects were randomised: 141 to LEO 90100, 135 to Calcipotriol plus BDP ointment, 49 to LEO 90100 vehicle and 51 to Ointment vehicle.

Diagnosis and main criteria for inclusion:
Hospital out-patients or patients attending the private practice of a board certified dermatologist, aged 18 years or above, with a diagnosis of psoriasis vulgaris of at least 6 months duration involving the trunk and/or limbs (2-30% of the Body Surface Area; BSA), amenable to treatment with a maximum of 90 g of trial medication per week, a disease severity of at least mild according to the IGA and a minimum Psoriasis Area and Severity Index (PASI) of at least 2 on the trunk and/or limbs. Women of childbearing potential had to have a negative pregnancy test at trial entry, and use a highly effective method of birth control during the trial.

Test product, dose and mode of administration, batch number:
LEO 90100, aerosol, foam (calcipotriol [as hydrate] 50 mcg/g plus betamethasone 0.5 mg/g [as dipropionate]), 30 g per can, applied once daily; Lot number: 113727401

Duration of treatment: Treatment lasted up to 4 weeks.

Reference therapy, dose and mode of administration, batch number:
Calcipotriol (as hydrate) 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) Ointment, 30 g per tube, applied once daily; Lot number: 120887101
LEO 90100 vehicle, 30 g per can, applied once daily; Lot number: 113727301
Ointment vehicle, 30 g per tube, applied once daily; Lot number: 120687101

Criteria for evaluation:
Efficacy was assessed by means of the IGA and the Investigator’s assessment of extent and severity of the clinical signs of psoriasis (redness, thickness and scaliness), and a modified Psoriasis Area and severity index (m-PASI excluding head) was calculated. Subjects’ assessment included Patient’s global assessment of disease severity, degree of itching by use of a Visual Analogue scale (VAS) and treatment satisfaction assessment using the Treatment Satisfaction Questionnaire of Medication (TSQM).
Primary response criterion: Subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’) for subjects with at least moderate disease at baseline, ‘clear’ for subjects with mild disease at baseline) according to the Investigators’ global assessment of disease severity on the trunk and limbs at week 4.

Secondary response criteria:
- Subjects with ‘controlled disease’ according to the IGA on the trunk and limbs at week 1.
- m-PASI at week 1.
- m-PASI at week 4.
- Subjects with PASI 50 (at least 50% reduction in m-PASI from baseline) at week 4.
- Subjects with PASI 75 (at least 75% reduction in m-PASI from baseline) at week 4.
- Subjects with ‘controlled disease’ (‘clear’ or ‘very mild’) according to the patients’ global assessment of disease severity at week 4.
- The change in itch as assessed by the Visual Analogue Scale from baseline to each subsequent visit.
- TSQM at end of treatment

Safety:
- Any reported adverse event
- Any reported adverse drug reaction
- Reasons for withdrawal from the study
- Change in albumin corrected serum calcium from baseline to week 4
- Change in urine calcium:creatinine ratio from baseline to week 4
- Change in vital signs (blood pressure, heart rate) from baseline to week 4
- Local safety and tolerability parameters

Statistical methods:
The Cochran-Mantel-Haenszel test was used to analyse the proportion of ‘Controlled disease’ according to the IGA at weeks 1 and 4, the PASI 50 and PASI 75 at week 4 and ‘Controlled disease’ according to the patient’s global assessment at week 4.

ANOVA methods were used to analyse m-PASI at week 1 and week 4 respectively including (pooled) centre, treatment and baseline m-PASI in the model. Also the change in VAS for itching at weeks 1, 2 and 4 was analysed including (pooled) centres, treatment groups, weeks and VAS at baseline in the model.

T-test or Wilcoxon test were used to compare the four TSQM scores at week 4.

SUMMARY - CONCLUSIONS

EFFECTIVENESS RESULTS:
- The proportion of ‘controlled disease’ at week 4 (primary endpoint) was 54.6% in the LEO 90100 group compared with 43.0% in the Calcipotriol plus BDP ointment group, 6.1% in the LEO 90100 vehicle group, and 7.8% in the Ointment vehicle group. LEO 90100 was superior to Calcipotriol plus BDP ointment in the treatment of psoriasis vulgaris over 4 weeks (OR 1.7; 95% CI 1.1 to 2.8; p=0.025).
The proportion of 'controlled disease' at week 1 was overall low; 3.6% in the LEO 90100 group, 6.1% in the Calcipotriol plus BDP ointment group, 2.0% in the LEO 90100 vehicle group, and 4.0% in the Ointment vehicle group. The statistical analysis of 'controlled disease' at week 1 showed no difference between LEO 90100 and Calcipotriol plus BDP ointment.

Both at week 4 and week 1, mean m-PASI scores were statistically significantly lower (indicating greater improvement) for LEO 90100 than for Calcipotriol plus BDP ointment (1.82 vs. 2.46, difference: -0.6, 95% CI -1.1 to -0.2, p=0.005 and 3.95 vs. 4.64, difference: -0.7, 95% CI -1.1 to -0.3, p=0.001, respectively).

The percentage of subjects with PASI 75 at week 4 and PASI 50 at week 4 was higher in the LEO 90100 group compared to the Calcipotriol plus BDP group (54.0% vs. 40.7% for PASI 75, and 80.9% vs. 74.8% for PASI 50) however the comparisons were not statistically significant.

According to the Patient's Global Assessment at week 4, similar proportion of subjects in the LEO 90100 group (61.6%) assessed their disease as 'controlled', as compared with the Calcipotriol plus BDP ointment group (59.8%) (OR 1.1; 95% CI 0.6 to 1.8; p=0.76).

There was a similar improvement in itching over time between the LEO 90100 and Calcipotriol plus BDP ointment groups.

Treatment satisfaction scores were overall higher in the LEO 90100 and the Calcipotriol plus BDP ointment groups than in the vehicle groups. There was no difference between the two active treatment groups.

SAFETY RESULTS:
- There were no deaths in the trial, and no SAEs or AEs leading to discontinuation in the LEO 90100 group. There were 3 SAEs and one AE that led to discontinuation in the Calcipotriol plus BDP ointment group; all were considered unrelated to study treatment.
- The incidence of AEs was comparable between the LEO 90100 and Calcipotriol plus BDP ointment groups, with 16 (11.3%) subjects in the LEO 90100 group and 14 (10.4%) subjects in the Calcipotriol plus BDP ointment group. Adverse drug reactions were reported for 1 (0.7%) subject in the LEO 90100 group and 4 subjects (3.0%) in the Calcipotriol plus BDP ointment group.
- There were no indications of effect on calcium homeostasis based on measurement of albumin-corrected serum calcium and spot urinary calcium/creatinine ratio.

CONCLUSIONS:
- LEO 90100 was more effective than Calcipotriol plus BDP ointment in the treatment of psoriasis vulgaris over 4 weeks.
- LEO 90100 was safe and well tolerated. The safety profile of LEO 90100 was comparable to that of Calcipotriol plus BDP ointment.

Date of the Report: 10-Jun-2013
### SCHEDULE/CHART OF TRIAL PROCEDURES

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[^1]: For women of childbearing potential a urine pregnancy test had to be performed at visit 1.
[^2]: Vital signs include blood pressure and heart rate.
[^3]: Physical examination was to as minimum include height and weight.
[^4]: Biochemistry and urinalysis included serum calcium, serum albumin, urine calcium and urine creatinine.
[^5]: For subjects prematurely withdrawn from treatment all trial procedures scheduled for Visit 4 was to be completed.
[^6]: If no washout was needed the subject could enter Visit 1 directly. Subjects entering Visit 1 without washout needed to have all trial procedures done applicable for screening visit.
[^7]: The treatment phase was followed by a FU phase if there was an on-going adverse event at the last on-treatment visit, which was classified as possible or probably related to the study medication or not assessable in relation to the study medication.
**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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