Clinical Study Report Synopsis

LEO 90100 in the Treatment of Psoriasis Vulgaris

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

A multi-centre, prospective, randomised, double-blind, 3-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**

<table>
<thead>
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<th>Name of Sponsor/Company:</th>
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<td>LEO Pharma A/S</td>
<td>Referring to Part of the Dossier</td>
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<th>Volume:</th>
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<td>LEO 90100, aerosol, foam</td>
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<th>Name of Active Ingredient:</th>
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<td>Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)</td>
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**Title of trial:**
A phase 2 study comparing treatment with LEO 90100 with betamethasone dipropionate in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle in subjects with psoriasis vulgaris.

**Investigators:** The international co-ordinating investigator was [REDACTED], MD, Department of Dermatology, The Mount Sinai School of Medicine, New York, USA.

**Trial centre(s):** The trial was conducted at 28 centres in the USA.

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

**Trial period (years):**
- First subject enrolled: 7-May-2012
- Last subject last visit: 10-Oct-012
- Phase of development: II

**Objectives:**
The primary objective was to compare the efficacy of treatment with LEO 90100 with betamethasone dipropionate (BDP) in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle for up to 4 weeks in subjects with psoriasis vulgaris on the trunk and limbs.

Secondary objectives were:
- To compare the safety of treatment with LEO 90100 with BDP in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle for up to 4 weeks in subjects with psoriasis vulgaris.
- To compare the efficacy of treatment with LEO 90100 with BDP in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle for up to 4 weeks in subjects with psoriasis vulgaris on the scalp.
- To compare the efficacy of treatment with LEO 90100 with BDP in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle at week 1 separately for each of the three areas: trunk and limbs; scalp; and trunk and limbs and scalp in subjects with psoriasis vulgaris.
- To compare the efficacy of treatment with LEO 90100 with BDP in LEO 90100 vehicle and calcipotriol in LEO 90100 vehicle for up to 4 weeks in subjects with psoriasis vulgaris on the trunk, limbs and scalp.

**Methodology:**
A multi-centre, prospective, randomised, double-blind, 3-arm, parallel group, 4-week trial in subjects with psoriasis vulgaris on the trunks and/or limbs and scalp. Eligible subjects were randomised in a 1:1:1 ratio to receive one of the following treatments:
- LEO 90100
- BDP in LEO 90100 vehicle
- Calcipotriol in LEO 90100 vehicle
The randomisation of subjects was stratified according to baseline severity (mild: at least moderate) as determined by the Investigator’s global assessment of disease severity (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. Trial medication was applied to all psoriatic lesions on the trunk, limbs and scalp once daily for up to 4 weeks. Concurrent anti-psoriatic treatments were not allowed, except for emollients and non-medicated shampoos. During the treatment phase, visits were performed as baseline (Day 0, Visit 1) and at week 1 (Visit 2), 2 (Visit 3) and 4 (Visit 4). Subjects classified as ‘clear’ on the trunk and limbs and/or scalp at Visit 2 or 3 were allowed to stop treatment on the cleared area 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):
A total of 300 subjects were planned; 100 subjects per treatment group. A total of 302 subjects were randomised: 100 to LEO 90100, 101 to BDP and 101 to calcipotriol.

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 and the scalp 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. Psoriasis on the trunk and/or limbs had to involve at least 2% of the Body Surface Area (BSA), psoriasis on the scalp at least 10% of the total scalp area, and total psoriatic involvement on the trunk, limbs and scalp not to exceed 50% BSA. 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 to psoriatic lesions on the trunk, limbs and scalp up to maximum 90 g of aerosol, foam per week.
Batch 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, aerosol, foam, 30 g per can, applied topically once daily;
Batch number: 113727101
Betamethasone 0.5 mg/g (as dipropionate) aerosol, foam; 30 g per can, applied topically once daily;
Batch number: 113727201
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)

Criteria for evaluation:

**Efficacy:**
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 psoriasis area and severity index (modified PASI, excluding face) was calculated. Three assessments were made: one for the trunk and limbs, one for the scalp and one overall assessment (i.e., the trunk, limbs and scalp). Subjects’ assessment included global assessment of disease severity, degree of itching by use of a Visual Analogue scale (VAS) and the health-related quality of life assessments using the Dermatology Life Quality Index (DLQI).

Primary response criterion: Subjects with ‘controlled disease’ (‘clear’ or ‘almost clear’ for subjects with at least moderate disease at baseline and ‘clear’ for subjects with mild disease at baseline) according to the IGA on the trunk and limbs at week 4.

Secondary response criterion: Subjects with ‘controlled disease’ according to the IGA on the trunk and limbs at week 1.

Further response criteria:
- Subjects with ‘controlled disease’ according to the IGA at week 4 on:
  1. Scalp
  2. Trunk and limbs and scalp
- Subjects with ‘controlled disease’ according to the IGA at week 1 on:
  1. Scalp
  2. Trunk and limbs and scalp

Response criteria involving m-PASI were analysed separately for the three areas; Trunk and limbs, Scalp, and Trunk and limbs and scalp
- 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
- The change in DLQI from baseline to each subsequent visit

**Safety:**
- Any reported adverse event
- Any reported adverse drug reaction
- 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
- Summary of Local Safety and Tolerability parameters
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
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Statistical methods:
For the primary analysis, the proportion of subjects who achieved 'controlled disease' according to the IGA at week 4 (LOCF) were compared between LEO 90100 and each of the other two treatments using the Cochran-Mantel-Haenszel test adjusting for the effect of (pooled) centre. For each of the treatment comparisons, the odds ratio (odds of 'Controlled disease' for LEO 90100 relative to that for each of the other treatments [Calcipotriol, BDP]), corresponding 95% confidence interval and a p-value were calculated. This approach was used for all binary response criteria.

For continuous response criteria, e.g. m-PASI at week 4, the treatment groups were compared using analysis of covariance including (pooled) centre, treatment and baseline value in the model.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:
Efficacy in psoriasis on the trunk and limbs
- The proportion of 'controlled disease' on the trunk and limbs at week 4 (LOCF) (primary endpoint) was 45.0% in the LEO 90100 group, 30.7% in the BDP group and 14.9% in the calcipotriol group. LEO 90100 aerosol foam was superior to both BDP in the aerosol foam vehicle (OR 1.81; 95% CI: 1.00 to 3.26; p=0.047) and calcipotriol in the aerosol foam vehicle (OR 4.34; 95% CI: 2.16 to 8.72; p<0.001). The results of the per protocol sensitivity analysis supported the results of analysis using the full analysis set.
- The proportion of 'controlled disease' on the trunk and limbs at week 1 (secondary endpoint) was overall low; 6% in the LEO 90100 group, 4% in the BDP and 2% in the calcipotriol group, and none of the comparisons were statistically significant.
- The results for m-PASI at week 4 supported the results for the primary endpoint. The mean m-PASI at week 4 was statistically significantly lower in the LEO 90100 group compared to BDP (p<0.001) and compared to calcipotriol (p<0.001). The percentage of subjects with PASI 75 at week 4 and with PASI 50 at week 4 was higher in the LEO 90100 group compared to BDP and calcipotriol (49.0%, 33.7%, 17.8% respectively for PASI 75 and 80.0%, 59.4%, 43.6% respectively for PASI 50).
  - With regard to m-PASI at week 1, LEO 90100 was statistically significantly more effective than calcipotriol (p=0.002) but the comparison to BDP was not statistically significant (p=0.11).

Efficacy in scalp psoriasis
- At week 4, the proportion of subjects who achieved 'controlled disease' (IGA) on the scalp was 53.0% in the LEO 90100 group, 47.5% in the BDP group and 35.6% in the calcipotriol group. LEO 90100 was superior to calcipotriol (OR 1.91, 95% CI 1.09 to 3.35; p=0.021) but the comparison to BDP was not statistically significant (OR 1.24; 95% CI 0.71 to 2.16; p=0.45).
- Results for m-PASI at week 4 were in line with the results for the IGA. LEO 90100 was statistically significantly more effective than calcipotriol (p<0.001) with regard to m-PASI at week 4 but the comparison to BDP was not statistically significant (p=0.058). The proportion of subjects with PASI 75 at week 4 and with PASI 50 at week 4 was higher in the LEO 90100 group compared to BDP and calcipotriol (73.0%, 65.3% and 50.5% for PASI 75 and 89.0%, 79.2% and 62.4% for PASI 50, respectively).
- At week 1, the proportion of 'controlled disease' (IGA) on the scalp was 26.0% in the LEO 90100 group, 13.9% in the betamethasone group and 7.9% in the calcipotriol group. LEO 90100 was superior to both BDP (OR 2.48; 95% CI 1.18 to 5.22; p=0.016) and calcipotriol (OR 4.13; 95% CI 1.69 to 10.09);
p<0.001). With regard to m-PASI at week 1, LEO 90100 was statistically significantly more effective than calcipotriol (p=0.037) but the comparison to BDP was not statistically significant (p=0.28).

Overall assessment of psoriasis on the trunk, limbs and scalp
- Results for the overall assessment of psoriasis on the trunk, limbs and scalp (IGA) generally mirrored the results for the trunk and limbs. At week 4, the proportion of subjects with ‘controlled disease’ on the trunk and limbs and scalp was 45.0% in the LEO 90100 group compared to 31.7% in the BDP group and 14.9% in the calcipotriol group. LEO 90100 was statistically significantly more effective than calcipotriol (OR 4.31, 95% CI 2.15 to 8.64; p<0.001) but not BDP (OR 1.71; 95% CI 0.96 to 3.02, p=0.063).
- LEO 90100 was statistically significantly more effective than BDP and calcipotriol with regard to m-PASI score at week 4 (both p<0.001). The proportion of subjects with PASI 75 at week 4 and with PASI 50 at week 4 was higher in the LEO 90100 group compared to BDP and calcipotriol (51.0%, 33.7% and 15.8% for PASI 75 and 84.0%, 59.4% and 46.5% for PASI 50).
- At week 1, the proportion of subjects with ‘controlled disease’ on the trunk and limbs and scalp was overall low (8% in the LEO 90100 group, 5% in the BDP group and 2% in the calcipotriol group), and none of the comparisons were statistically significant. With regard to m-PASI at week 1, LEO 90100 was statistically significantly more effective than calcipotriol (p=0.001) but the comparison to BDP was not statistically significant (p=0.090).

Patient reported outcomes
- The proportion of ‘controlled disease’ according to Patients’ global assessment of disease severity at week 4 (LOCF) was 60.0% in the LEO 90100 group, 40.6% in the BDP group and 29.7% in the calcipotriol group. LEO 90100 aerosol foam was more effective than BDP (OR 2.23; 95% CI: 1.26 to 3.97; p=0.005) and calcipotriol (OR 3.74; 95% CI: 2.02 to 6.91; p=0.001).
- LEO 90100 was statistically significantly more effective in relieving itching than calcipotriol at all post baseline visits, and had similar efficacy to BDP.
- LEO 90100 was statistically significantly more effective in improving health related quality of life as assessed using the DLQI than calcipotriol at all post baseline visits (p<0.001 at each visit), and had similar efficacy to BDP.

SAFETY RESULTS:
- There were no deaths in the trial. One SAE of hypersensitivity was reported in the LEO 90100 group, which was considered related to study treatment. Adverse events led to discontinuation of 2 subjects in the LEO 90100 group (including the subject with SAE) and 2 subjects in the calcipotriol group.
- The overall incidence of AEs was low and comparable between the treatment groups, with 11 (11%) of subjects in the LEO 90100 group, 13 (13.1%) in the BDP group and 10 (10.1%) in the calcipotriol group. Adverse drug reactions (i.e., AEs for which the causal relationship to the drug cannot be ruled out) were reported for 4 (4%) subjects in the LEO 90100 group, 7 (7.1%) in the BDP group and 6 (6.1%) in the calcipotriol group.
- There was no indication of an effect on calcium homeostasis based on measurement of albumin-corrected serum calcium and spot urinary calcium:creatinine ratio.

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Overall assessment of psoriasis on the trunk, limbs and scalp
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**OVERALL CONCLUSIONS:**

- LEO 90100 aerosol foam was superior to both betamethasone dipropionate and calcipotriol in the aerosol foam vehicle in the treatment of psoriasis vulgaris on the trunk and limbs over 4 weeks.
- LEO 90100 aerosol foam was more effective than calcipotriol in the aerosol foam vehicle but not different from betamethasone dipropionate in the aerosol foam vehicle in the treatment of psoriasis vulgaris on the scalp over 4 weeks.
- LEO 90100 was safe and well tolerated.

**Date of the Report:** DRAFT 12-APR-2012
## Schedule/Chart of Trial Procedures

<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening</th>
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<th>2&lt;sup&gt;nd&lt;/sup&gt;</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt;</th>
<th>4&lt;sup&gt;th&lt;/sup&gt;</th>
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<td>14 ±2 Day</td>
<td>28 ±2 Day</td>
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<td>X</td>
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<tr>
<td>Visit window / Day</td>
<td>Screening</td>
<td>1(^1)</td>
<td>2(^1)</td>
<td>3(^1)</td>
<td>4</td>
<td>FU(^7), if required</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Week -4 to 0</td>
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<td>1</td>
<td>2</td>
<td>4</td>
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<td>2 weeks after last visit</td>
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<td>End of trial Form(^5)</td>
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\(^1\) For women of childbearing potential a urine pregnancy test had to be performed at visit 1.
\(^2\) Vital signs included 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 had 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 ongoing 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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