Clinical Study Report Synopsis

LEO 90100 compared to vehicle in subjects with psoriasis vulgaris

A phase 3 trial comparing once daily treatment with LEO 90100 calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) with vehicle in subjects with psoriasis vulgaris

A multi-centre, prospective, randomised, double-blinded, 2-arm, parallel group, 4-week trial in subjects with psoriasis vulgaris

LEO 90100 in PSOriasis vulgaris, a Four weeks, vehicle controlled, efficacy And Safety Trial - the PSO-FAST trial

LEO Pharma A/S
Clinical Development and Safety

LP0053-1001
Report Date 04-Mar-2014
EudraCT Number: N/A
Clinical Study Report Synopsis Statement

Approval Statement, Sponsor

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

- Biostatistics and Data Management
- Medical Department

Approval Statement, Investigator

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:

- , MD

International Co-ordinating Investigator
## SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>LEO Pharma A/S</th>
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<tr>
<td>Name of Finished Product:</td>
<td>LEO 90100 aerosol foam</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)</td>
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<tr>
<td>Title of Trial:</td>
<td>A phase 3 trial comparing once daily treatment with LEO 90100 calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) with vehicle in subjects with psoriasis vulgaris</td>
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<td>Investigators:</td>
<td>The international coordinating investigator was [redacted], MD, Central Dermatology, 1034 S, Brentwood Blvd., Suite 600, St. Louis, MO 63117, USA.</td>
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<td>Trial Centres:</td>
<td>27 trial centres in the USA.</td>
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<td>Publication(s) based on the trial:</td>
<td>None at the time of this clinical study report.</td>
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<td>Phase of Development:</td>
<td>3</td>
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<td>Objectives:</td>
<td>Primary Objective: To compare the efficacy of treatment with LEO 90100 to that of treatment with vehicle for up to 4 weeks in subjects with psoriasis vulgaris. Secondary Objectives: To compare the safety of treatment with LEO 90100 to that of treatment with vehicle for up to 4 weeks in subjects with psoriasis vulgaris.</td>
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<td>Methodology:</td>
<td>Trial LP0053-1001 was a multi-centre, prospective, randomised, double-blinded, 2-arm, parallel group trial comparing the efficacy and safety of treatment with LEO 90100 to that of treatment with vehicle in subjects with psoriasis vulgaris. Approximately 400 subjects who fulfilled all inclusion and exclusion criteria were planned to be randomised in a 3:1 ratio to receive up to 4 weeks' treatment once daily with either LEO 90100 (300 subjects) or vehicle (100 subjects) on psoriasis lesions on the trunk and/or limbs. The randomisation of subjects was stratified by site. The trial consisted of a wash-out/screening period for up to 4 weeks (28 days) for withdrawal of pre-trial medication, a 4-week treatment period (Visits 1 to 4) and, if required, a 2-week safety follow-up period. Efficacy assessments included the Investigator’s Global Assessment of disease severity (IGA) and the modified Psoriasis Area and Severity Index (m-PASI). For the IGA, the (sub)investigator made a global assessment of the disease severity of the psoriasis vulgaris on the trunk and limbs, which represented the average lesion severity on the trunk and limbs. For the m-PASI, the (sub)investigator assessed the extent and severity of the three clinical signs (redness, thickness, and scaliness) on the arms, trunk and legs. Subjects classified as ‘clear’ according to the IGA on the trunk and limbs at either Visit 2 or Visit 3 were allowed to stop treatment at the (sub)investigator’s discretion. Should such occur, the subject was to remain in the trial and attend all scheduled visits. If the psoriasis reappeared on the treatment areas, the subject was to reinitiate treatment without consulting the (sub)investigator. More than one discontinuation/restart cycle was allowed. Safety assessments included recordings of vital signs, adverse events (AEs), and local safety and tolerability assessments. Blood and spot urine samples were taken for evaluation of albumin-corrected serum calcium level and calcium:creatinine ratio, respectively.</td>
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<td>Number of Subjects (Planned and Analysed):</td>
<td>400 subjects were planned to be randomised in a 3:1 ratio, i.e. 300 subjects in the LEO 90100 treatment group and 100 in the vehicle group. In total, 426 subjects were randomised; 323 to LEO 90100 and 103 to vehicle.</td>
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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)

Diagnosis and Main Criteria for Inclusion:
The trial population was chosen to include subjects ≥ 18 years of age with psoriasis vulgaris on the trunk and/or limbs of at least mild severity according to the Investigator’s Global Assessment of Disease Severity (IGA) and amenable to topical therapy with up to 90 g of trial medication per week. The eligibility criteria prevented confounding issues with diagnosis and eliminated any possible effect of concurrent diseases or concomitant medications on clinical assessment.

Investigational Product, Dose and Mode of Administration, Batch Number:
- LEO 90100 aerosol foam (LEO 90100) (calcipotriol 50 mcg/g and betamethasone 0.5 mg/g, as dipropionate); Lot number: 123127301

The investigational product was applied to psoriasis vulgaris affected areas on the trunk, arms, and legs once daily according to random assignment (see Methodology section above).

Duration of Treatment:
4 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number:
- Aerosol foam vehicle (vehicle); Lot number: 123087102

The investigational product was applied to psoriasis vulgaris affected areas on the trunk, arms, and legs once daily according to random assignment (see Methodology section above).

Criteria for Evaluation:
Efficacy assessments
Primary endpoint:
- Subjects with ‘treatment success’ (‘clear’ or ‘almost clear’ for subjects with at least moderate disease at baseline, ‘clear’ for subjects with mild disease at baseline) according to the IGA at Week 4.

Secondary endpoints:
- m-PASI at Week 4
- m-PASI at Week 1

Safety:
- Any reported adverse event (AE)
- Any reported adverse drug reaction (ADR)
- Change in albumin-corrected serum calcium from baseline to Week 4
- Change in urine calcium:creatinine ratio from baseline to Week 4

Statistical Methods:
Primary endpoint:
The primary endpoint was analysed for the full analysis set and the per protocol analysis set. The analysis for the full analysis set was regarded as primary while the analysis for the per protocol analysis set was supportive. Multiple imputation of IGA values was carried out and for each imputed dataset, the odds ratio of ‘treatment success’ at Week 4 for LEO 90100 relative to vehicle was estimated by calculating the Mantel-Haenszel odds ratio adjusted for pooled centres and its 95% confidence interval. Combined inference was obtained using Rubin’s pooling methodology.

Secondary endpoints:
The secondary endpoints were analysed for the full analysis set. Multiple imputation of m-PASI values was carried out. LEO 90100 and vehicle were compared using an analysis of variance (ANOVA) including (pooled) centre, treatment and baseline m-PASI in the model. The adjusted difference between LEO 90100 and vehicle and the corresponding p-value as well as a 95% confidence interval were calculated. Sensitivity analyses excluding Site (see Study Population section below) were conducted for all PASI endpoints.
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Summary of Results and Conclusions

Study Population:
In total, 491 subjects were screened, among whom 65 were screening failures. The remaining 426 subjects were randomised; 323 to LEO 90100 and 103 to vehicle. All 426 randomised subjects received treatment with investigational product. In total, 14 of the randomised subjects withdrew from the trial and 412 (97%) subjects completed the trial. The most common reason for withdrawal was ‘lost to follow-up’ (8 subjects).

Overall, demographics and disease-related characteristics at baseline were in line with the targeted trial population. All subjects were ≥ 18 years of age, fulfilled eligibility requirements to a minimum duration of psoriasis vulgaris of 6 months (range: 1-67 years), a BSA of 2 to 30% (range: 2-30%), an IGA of at least ‘mild’ in severity, and an m-PASI score of at least 2 (range 2-47).

All 426 randomised and treated subjects were included in the full analysis set and safety analysis set. Important protocol deviations were identified for 28 subjects and their data were therefore excluded from the per protocol analysis set. The per protocol analysis set thus comprised 398 subjects.

Note: One site (confirmed by signature of a protocol deviation that the extent scores for the m-PASI assessment might not have been conducted as per protocol at this site. Consequently, sensitivity analyses excluding Site were conducted for all PASI endpoints.

At all on-treatment visits, the subject was asked if she/he has used the investigational product as prescribed. Compliance with treatment instructions for the assigned investigational product was comparable between treatment groups.

Summary of Efficacy Results:

Primary Endpoint
- The proportion of subjects achieving ‘treatment success’ at Week 4 was 53.3% in the LEO 90100 group and 4.8% in the vehicle group (applying multiple imputation for missing data). LEO 90100 was statistically significantly more effective than vehicle (OR 30.3; 95% CI 9.7 to 94.3; p<0.001). The sensitivity analyses applying LOCF for missing data, the vehicle-based multiple imputation analysis, the non-responder imputation analysis, the analysis for observed cases, and the per protocol analysis supported the results of the primary analysis.

Secondary Endpoints
- When adjusting for the effect of pooled centres and baseline m-PASI, the mean m-PASI at Week 4 was 2.0 in the LEO 90100 group and 5.3 in the vehicle group (applying multiple imputation for missing data) with a statistically significant difference between treatments (mean difference -3.3; 95% CI: -3.9 to -2.7; p<0.001), thereby supporting the outcome of the analysis of the primary endpoint.
- A reduction in mean m-PASI score was seen as early as Week 1 and LEO 90100 was statistically significantly more effective than vehicle (mean difference -1.3; 95% CI -1.8 to -0.8; p<0.001) at this time-point (applying multiple imputation for missing data).
- The sensitivity analyses applying LOCF for missing data, the vehicle-based multiple imputation analysis, the non-responder imputation analysis and the analysis for observed cases supported the results of the primary analysis. For the sensitivity analyses excluding Site the overall conclusions were unaltered.

Tertiary Endpoints – Investigator’s Assessments
- In the LEO 90100 group, the proportion of subjects achieving ‘treatment success’ increased as the trial progressed (Week 1: 8.5%; Week 2: 26.3%; Week 4: 53.4%), while 1.0%, 2.0%, and 4.0% of subjects allocated to the vehicle group obtained ‘treatment success’ at Week 1, Week 2, and Week 4, respectively.
- The percentage of subjects with a 50% reduction in PASI at Week 4 was estimated at 82.3% in the LEO 90100 group and 28.0% in the vehicle group. LEO 90100 was statistically significantly more effective than vehicle (OR 13.9; 95% CI 7.6 to 25.7; p<0.001). Similar findings were obtained for the sensitivity analyses excluding Site.
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Tertiary Endpoints – Investigator’s Assessments (continued)
- The percentage of subjects with a 75% reduction in PASI at Week 4 was estimated as 52.9% in the LEO 90100 group and 8.2% in the vehicle group. LEO 90100 was statistically significantly more effective than vehicle (OR 14.9; 95% CI 6.5 to 34.0; p<0.001). Similar findings were obtained for the sensitivity analyses excluding Site...
- At baseline, the severity of clinical signs of the target lesion was evaluated as ‘moderate’ or ‘severe’ in approximately 80-90% of subjects with no notable differences between treatment groups. In the LEO 90100 group, the severity of target lesions decreased during the course of the trial and at Week 4, the redness, thickness, and scaliness of the target lesion had disappeared completely in 32.6%, 57.5%, and 70.0% of subjects, respectively. The corresponding rates in the vehicle group were 3.0%, 4.0%, and 18.2%, respectively.
- At Week 4, the mean decrease from baseline in percentage BSA involvement of psoriasis on the trunk and limbs (excluding skin folds and genitals) was 3.7%-points (baseline mean 7.4%) in the LEO 90100 group and 1.0%-points (baseline mean 8.0%) in the vehicle group.

Tertiary Endpoints – Subject’s Assessments
- Overall, the results for subject’s assessments of disease severity were in line with those of the investigator. In the LEO 90100 group, the proportion of subjects achieving ‘treatment success’ increased as the trial progressed (Week 1: 21.9%; Week 2: 42.2%; Week 4: 65.2%), while 17.6%, 21.8%, and 22.2% of subjects allocated to the vehicle group obtained ‘treatment success’ at Week 1, Week 2, and Week 4, respectively. At Week 4, LEO 90100 was statistically significantly more effective than vehicle (OR 7.9; 95% CI 4.4 to 14.1; p<0.001).
- Subjects assessed itching as increasingly less severe during the course of the trial, particularly in the LEO 90100 group. At Week 4, the mean change from baseline (adjusted for pooled centres and baseline score) in itch (VAS) was -43.1 in the LEO 90100 group and -22.7 in the vehicle group. LEO 90100 was statistically significantly more effective than vehicle at all visits. In the LEO 90100 group, 110 subjects (36.8%) achieved 70% itch reduction on Day 3. Responder rates in the LEO 90100 group increased successively during the course of the trial, and at Week 4, 248 subjects (83.5%) had obtained 70% itch reduction versus 39 subjects (40.6%) in the vehicle group. The odds ratio for achieving 70% reduction in itch in the LEO 90100 group relative to the vehicle group (adjusted for pooled centres) was statistically significant at all visits.
- Subjects assessed itch-related sleep loss as increasingly less severe during the course of the trial, particularly in the LEO 90100 group. At Week 4, the mean change from baseline (adjusted for pooled centres and baseline score) in itch-related sleep loss (VAS) was -21.9 in the LEO 90100 group and -10.0 in the vehicle group. LEO 90100 was statistically significantly more effective than vehicle at all visits. In the LEO 90100 group, 87 subjects (35.5%) achieved 70% reduction on Day 3. Responder rates in the LEO 90100 group increased successively during the course of the trial, and at Week 4, 172 subjects (70.8%) had obtained 70% reduction in itch-related sleep loss versus 33 (39.8%) in the vehicle group. The odds ratio for achieving 70% reduction in itch-related sleep loss in the LEO 90100 group relative to the vehicle group (adjusted for pooled centres) was statistically significant at all visits.
- Statistically significantly greater improvement in quality of life (as measured by DLQI) was demonstrated for LEO 90100 versus vehicle at all visits (p<0.001).
- For EQ-5D-5L, subjects evaluated significantly improvements for the dimension pain/discomfort. In the LEO 90100 group, the proportion of subjects evaluating their pain/discomfort as non-existing increased from 30.1% at baseline to 68.4% at Week 4, and the difference between treatment groups was statistically significant (p<0.001) at Week 4.

Summary of Safety Results:
- There were no deaths in the trial. Two SAEs occurred in the trial and were reported in the LEO 90100 group, both assessed as having no relation to investigational product. One of the SAEs led to discontinuation of treatment. There were no AEs leading to withdrawal of the subject from the trial. The vast majority of the AEs were mild or moderate and only 5 AEs were rated as severe. The severe AEs were reported in the LEO 90100 group.
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Summary of Safety Results (continued):
- The overall incidence of AEs was low and comparable between treatment groups, with 51 (15.8%) subjects in the LEO 90100 group and 12 (11.7%) subjects in the vehicle group. ADRs (i.e. AEs for which the causal relationship to the drug cannot be ruled out) were reported for 10 subjects (3.1%) in the LEO 90100 group and 2 subjects (1.9%) in the vehicle group. Lesional/perilesional AEs were reported for 9 subjects (2.8%) in the LEO 90100 group and 3 subjects (2.9%) in the vehicle group. Local reactions, as assessed by application site scores, were few and occurred with similar frequency in the 2 treatment groups. The majority of local reactions were erythema, dryness, and burning/pain of mild to moderate intensity.
- There were no significant changes in albumin-corrected serum calcium and spot urinary calcium:creatinine ratio.

Conclusion:
- Superiority of LEO 90100 compared to vehicle in the treatment of psoriasis vulgaris on the trunk and limbs over 4 weeks was confirmed.
- It was confirmed that LEO 90100 was safe and well tolerated in the treatment of psoriasis vulgaris on the trunk and limbs over 4 weeks.