Clinical Study Report Synopsis

A psoriasis plaque test trial with LP0113 spray
in patients with psoriasis vulgaris

Design of trial:

A phase 2a trial evaluating the anti-psoriatic effect of LP0113 aerosol spray compared with its vehicle and with Daivobet® gel, LEO 90100 aerosol foam, betamethasone dipropionate aerosol spray and calcipotriol aerosol spray in the treatment of psoriasis vulgaris

A single centre, investigator-blinded, within subject randomised, active- and vehicle-controlled, 4 weeks, repeated dose trial

The clinical trial, including the archival of essential documents, was conducted in compliance with the clinical trial protocol, GCP, and the applicable regulatory requirement(s).
Clinical Trial Report Synopsis Statement

Approval Statement, LEO Pharma A/S

The following persons have approved this clinical study report synopsis using electronic signatures as presented on the last page of this document:

[Signature], MSc Stat
[Signature], Global Clinical Operations

Approval Statement, Coordinating Investigator

The coordinating investigator approves the clinical study report synopsis by manually signing the International Coordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to the clinical study report.

The following person has approved this clinical study report synopsis:

[Signature], MD
Coordinating investigator
### Trial Registration Number

| NCT02416258 | EudraCT number | 2014-004759-30 |

### Title of Trial

A psoriasis plaque test trial with LP0113 spray in patients with psoriasis vulgaris

### Investigators

This was a single centre trial. [Redacted], MD, France was appointed as signatory investigator

### Trial Centres

See above.

### Publications

None at the time of the final clinical trial report.

### Clinical Trial Period

| Date of First Subject First Visit: 02-Apr-2015 | Date of Last Subject Last Visit: 30-Jun-2015 |

### Development Phase

Phase 2a

### Objectives

The primary objective of the trial was to evaluate the anti-psoriatic effect of LP0113 compared to Daivobet® gel, LEO 90100, betamethasone dipropionate (BDP) in the aerosol spray vehicle, calcipotriol in the aerosol spray vehicle, and aerosol spray vehicle.

The secondary objective of the trial was to obtain information on local tolerability of LP0113 compared to Daivobet® gel, LEO 90100, BDP in the aerosol spray vehicle, calcipotriol in the aerosol spray vehicle, and aerosol spray vehicle.

### Methodology

This was a single centre, investigator-blinded, within-subject, randomised, active- and vehicle-controlled, 4 weeks, repeated dose trial.

Each subject received 6 treatments (LP0113 aerosol spray [LP0113], LEO 90100 aerosol foam [LEO 90100], Daivobet® gel, calcipotriol in the aerosol spray vehicle, BDP in the aerosol spray vehicle, and aerosol spray vehicle), and each treatment was allocated randomly to a 5 cm² test site. Test sites were located within 1 to 6 stable psoriasis lesions (target plaques) on arms, legs and/or trunk and delineated with a disposable circular device.

Subjects had 26 visits (6 days per week) to the trial site. Treatment applications were performed by site staff at each visit, with the exception of the last visit which did not include any applications. A blinded investigator assessed test sites twice weekly for the severity of the clinical signs erythema, scaling, and infiltration. Ultrasound measurements of skin thickness were done at Baseline (Day 1) and end of treatment (Day 29). A safety follow-up visit was scheduled 14 (±2) days after the last on-treatment visit, if required.

### Number of Subjects Planned and Analysed

50 subjects were planned and 50 subjects were allocated to treatment (all subjects received all 6 treatments).

### Diagnosis and Main Criteria for Inclusion

- Age 18 years or above
- Subjects with a diagnosis of psoriasis vulgaris with lesions located on arms, legs and/or trunk. The lesions must have a total size suitable for application of 6 different products.
- Subjects with, in the opinion of the investigator, stable psoriasis based on Total Plaque Score evaluated at Screening visit and rechecked at Baseline. The score of each clinical sign (erythema, scaling, infiltration) was not allowed to change more than 1 point between the 2 visits.
- Subjects with psoriasis lesions (plaques) assessed by a Total Plaque Score (sum of scores of erythema, scaling and infiltration) of 4 to 9 inclusive but each individual item ≥ 1.
**Test Product, Dose and Mode of Administration, Batch Number**
LP0113 (calcipotriol 50 mcg/g and betamethasone [as dipropionate] 0.5 mg/g); 50 mg degassed spray was applied once daily to 1 test site 6 days a week; batch number: P14065

**Duration of Treatment**
Wash-out up to 4 weeks, treatment for 4 weeks, follow-up 2 weeks after last visit, if required.

**Reference Product, Dose and Mode of Administration, Batch Number**
- Daivobet® gel (calcipotriol 50 mcg/g and betamethasone [as dipropionate] 0.5 mg/g); 50 µl gel applied once daily to 1 test site 6 days a week; batch number: 133007101
- LEO 90100 (calcipotriol 50 mcg/g and betamethasone [as dipropionate] 0.5 mg/g); 50 mg degassed foam applied once daily to 1 test site 6 days a week; batch number: P14035
- BDP in the aerosol spray vehicle (betamethasone [as dipropionate] 0.5 mg/g); 50 mg degassed spray was applied once daily to 1 test site 6 days a week; batch number: P14068
- Calcipotriol in the aerosol spray vehicle (calcipotriol 50 mcg/g); 50 mg degassed spray was applied once daily to 1 test site 6 days a week; batch number: P14067
- Aerosol spray vehicle (no active ingredients); 50 mg degassed spray was applied once daily to 1 test site 6 days a week; batch number: P14066

**Criteria for Evaluation**

**Primary Endpoint**
The primary endpoint was absolute change in total clinical score (TCS) of clinical signs (sum of erythema, scaling, and infiltration) at end of treatment compared to Baseline.

The severity of the clinical signs erythema, scaling, and infiltration was assessed on a 7-point scale ranging from 0 (no evidence) to 3 (severe). The TCS was obtained by summing the scores for erythema, scaling, and infiltration and ranged from 0 to 9.

**Secondary Endpoints**
- Absolute change in TCS at individual visits compared to Baseline.
- Absolute change in score of each clinical sign: erythema, scaling, infiltration at end of treatment and at individual visits compared to Baseline.
- Absolute change in total skin thickness and echo-poor band thickness at end of treatment compared to Baseline.

**Safety Evaluation**
Any reported adverse events (AE), including AEs assessed to be related to the investigational medicinal product (IMP) by the investigator.

**Statistical Methods**

**Primary Endpoint:**
The absolute change in TCS from Baseline to end of treatment was analysed using a 2-way analysis of variance (ANOVA) with treatment and subject as fixed effects. Treatment differences were tested as contrasts. 95% confidence intervals (CI) of differences between treatments were calculated. No correction to multiplicity was made in the primary analysis. A secondary analysis using Tukey’s honestly significant difference (HSD) method for correcting p-values was produced in the 2-way ANOVA.

**Secondary Endpoints:**
Changes in TCS as well as changes in erythema, scaling, and infiltration from Baseline to end of treatment were tabulated. The absolute change in total skin thickness and echo-poor band thickness from Baseline to end of treatment were compared between treatments using a 2-way ANOVA with treatment and subject as fixed effects. 95% CIs of differences between treatments were calculated. A secondary analysis using Tukey’s HSD method for correcting p-values was produced in the 2-way ANOVA. For each subject and test site, the mean of 3 measures per visit (total skin thickness, echo-poor band thickness) were used in the analyses.
Summary of Results

Efficacy Results

Primary Endpoint

- The largest mean numeric change in TCS from Baseline to end of treatment was observed for test sites treated with LEO 90100 (mean change -5.9), followed by LP0113 (-5.4), BDP in the aerosol spray vehicle (-5.2), Daivobet® gel (-5.0), calcipotriol in the aerosol spray vehicle (-3.1), and aerosol spray vehicle (-1.6).

- Statistically significant treatment differences (differences in absolute change in TCS from Baseline to end of treatment) in favour of LP0113 were found when LP0113 was compared with calcipotriol in the aerosol spray vehicle (mean difference -2.28; 95% CI -2.77 to -1.79; p<0.001) and the aerosol spray vehicle (mean difference -3.81; 95% CI -4.30 to -3.32; p<0.001). A comparison of LP0113 and LEO 90100 showed a statistically significant treatment difference in favour of LEO 90100 (mean difference 0.55; 95% CI 0.06 to 1.04; p=0.028).

- A secondary analysis using Tukey’s HSD method for correcting p-values supported the primary analysis (significant treatment difference between LP0113 and calcipotriol in the aerosol spray vehicle and between LP0113 and the aerosol spray vehicle) but showed a non-significant treatment difference between LP0113 and LEO 90100 (95% CI -0.17 to 1.27; p=0.24).

- In both the primary and secondary analyses, LEO 90100 was found to be significantly more efficacious than the 4 other comparators (aerosol spray vehicle, calcipotriol in the aerosol spray vehicle, BDP in the aerosol spray vehicle, and Daivobet® gel).

Secondary Endpoints

- Mean numeric changes in TCS from Baseline were larger in the LP0113 group than the BDP in aerosol spray group and the Daivobet® gel group from Day 8 to end of treatment. Mean numeric changes in TCS from Baseline were larger in the LP0113 group than the calcipotriol in the aerosol spray vehicle group and the aerosol spray vehicle group at all time-points. Mean numeric changes in TCS from Baseline were larger in the LEO 90100 group than in all other groups at all time-points.

- Scaling and infiltration scores followed the same pattern as the TCS, with larger mean numeric changes from Baseline in the LP0113 group than the BDP in aerosol spray group and the Daivobet® gel group from Day 8 to end of treatment. For all 3 clinical signs (erythema, scaling, infiltration), larger mean numeric changes were observed in the LP0113 group than the calcipotriol in the aerosol spray vehicle group and the aerosol spray vehicle group at all time-points. Mean numeric changes from Baseline were larger in the LEO 90100 group than in all other groups at all time-points for all clinical signs (erythema, scaling, infiltration).

- Statistically significant treatment differences in total skin thickness in favour of LP0113 were observed when LP0113 was compared with calcipotriol in the aerosol spray vehicle (mean difference -0.49 mm; 95% CI -0.62 to -0.35; p<0.001) and the aerosol spray vehicle (mean difference -0.82 mm; 95% CI -0.95 to -0.68; p<0.001). No statistically significant differences were found when LP0113 was compared with BDP in the aerosol spray vehicle (mean difference -0.00 mm; 95% CI -0.14 to 0.13; p=0.95), Daivobet® gel (mean difference -0.07 mm; 95% CI -0.21 to 0.06; p=0.29), or LEO 90100 (mean difference 0.06 mm; 95% CI -0.07 to 0.20; p=0.35).

- Statistically significant treatment differences (differences in echo-poor band thickness from Baseline to end of treatment) in favour of LP0113 were observed when LP0113 was compared with calcipotriol in the aerosol spray vehicle (mean difference -0.86 mm; 95% CI -1.03 to -0.68; p<0.001). No statistically significant differences were found when LP0113 was compared with BDP in the aerosol spray vehicle (mean difference -0.04 mm; 95% CI -0.22 to 0.13; p=0.62), Daivobet® gel (mean difference -0.10 mm; 95% CI -0.27 to 0.08; p=0.28), or LEO 90100 (mean difference 0.06 mm; 95% CI -0.12 to 0.23; p=0.52).

- LEO 90100-treated test sites had significantly larger reductions in both total skin thickness and echo-poor band thickness than calcipotriol in the aerosol spray vehicle (p<0.001) and the aerosol spray vehicle (p<0.001).

- Secondary analyses of total skin thickness and echo-poor band thickness data using Tukey’s HSD method for correcting p-values were generally in agreement with the primary analyses.
### Safety Results

A total of 18 subjects (36.0%) experienced a total of 25 AEs after start of treatment with IMPs. No deaths, other serious adverse events (SAEs), AEs assessed by the investigator to be related to the trial treatments, or AEs leading to withdrawal were observed. No cutaneous AEs were observed.

The most frequent AE was headache (4 [8.0%] subjects) with migraine, diarrhoea, back pain, neck pain, and oropharyngeal pain each being reported by 2 (4.0%) subjects. All other AEs were reported by 1 subject.

The majority of the AEs were mild, with 9 AEs in 8 subjects rated as moderate by the investigator. No severe AEs were observed in this trial.

The treatments were well tolerated in this population.

### Conclusion

This plaque test trial in 50 subjects showed that LP0113 was statistically significantly more effective after 4 weeks than calcipotriol in the aerosol spray vehicle and the aerosol spray vehicle in subjects with psoriasis vulgaris. LEO 90100 was more efficacious than all other treatments after 4 weeks, including LP0113. LP0113 was found to be well-tolerated by the subjects.
**ELECTRONIC SIGNATURES**

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