Clinical Study Report Synopsis

A psoriasis plaque test trial with LEO 90100 compared to Betesil® in patients with psoriasis vulgaris

A phase 2a trial evaluating the anti-psoriatic effect of LEO 90100 aerosol foam compared to Betesil® medicated plaster in the treatment of psoriasis vulgaris

Design of trial:
A single centre, investigator-blinded, within subject controlled, randomised, intra-individual comparison, 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).

LEO Pharma A/S

Trial ID: LP0053-1227
Date: 31-May-2016
Version: Final
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

[Signature], MD, PhD
[Signature], Medical Science and Safety

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
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**Title of Trial**
A psoriasis plaque test trial with LEO 90100 compared to Betesil® 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:** 22-Sep-2015
- **Date of Last Subject Last Visit:** 07-Dec-2015
- **Development Phase:** Phase 2a

**Objectives**
The primary objective of the trial was to evaluate the anti-psoriatic effect of LEO 90100 compared with Betesil® medicated plaster.
The secondary objective of the trial was to evaluate the local tolerability of LEO 90100 compared with Betesil® medicated plaster.

**Methodology**
This was a single centre, investigator-blinded, randomised, intra-individual comparison, 4 weeks, repeated dose trial.
Each subject received 2 treatments (LEO 90100 aerosol foam; Betesil® medicated plaster), each applied to 3 test sites. Test sites were located within 2 or 3 stable psoriasis lesions on arms, legs and/or trunk and delineated with a disposable circular device. Treatments were allocated randomly but always pair-wise within each plaque. Site staff performed all applications.
Subjects had 26 visits (6 days per week) to the trial site. 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**
According to the protocol, 35 subjects were planned and 35 subjects were allocated to treatment (all subjects received both treatments).

**Diagnosis and Main Criteria for Inclusion**
- Age 18 years or above
- Subjects with a diagnosis of psoriasis vulgaris with at least 2, preferably 3, lesions located on arms, legs and/or trunk. For subjects with 3 lesions, each lesion should have a size suitable to accommodate 2 test sites (test site area 5 cm², distance between 2 test sites at least 2 cm). For subjects with 2 lesions, one lesion should have a size suitable to accommodate 4 test sites, and the other lesion should accommodate 2 test sites.
- Subjects with, in the opinion of the investigator, stable psoriasis based on Total Plaque Score evaluated at the Screening Visit and re-checked at Baseline. The score of each clinical sign (erythema, scaling, infiltration) should not 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 (both included) but each individual item should have a score of ≥ 1.
**Test Product, Dose and Mode of Administration, Batch Number**
LEO 90100 aerosol foam (calcipotriol 50 mcg/g and betamethasone [as dipropionate] 0.5 mg/g); 50 mg degassed foam applied once daily to each test site 6 days a week; batch number B2200-01.

**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**
Betesil® medicated plaster; each medicated plaster (7.5 cm x 10 cm) contains 2.25 mg of betamethasone valerate (corresponding to 1.845 mg of betamethasone); plasters were cut to fit the area of the test site (5 cm²) and applied once daily, 6 days a week; batch number B2201-01.

**Criteria for Evaluation**

**Primary Endpoint**
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 had a range 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 study medication by the investigator.

**Statistical Methods**

**Primary Endpoint**: The absolute change in TCS from Baseline to end of treatment was analysed using a mixed model analysis of variance (ANOVA) with treatment as fixed effect and subject as random effect. The 95% confidence interval (CI) of the difference between treatments was calculated.

**Secondary Endpoints**: The absolute change in total skin thickness and echo-poor band thickness from Baseline to end of treatment were compared between treatments using a mixed model ANOVA with treatment as fixed effect and subject as random effect. The 95% CI of the difference between treatments was calculated.

No adjustments for multiplicity were performed on secondary endpoints since these were supportive for the primary endpoint.

**Summary of Results**

**Trial Population**
35 subjects were treated with at least one application/dose of LEO 90100 and Betesil® medicated plaster; 1 subject discontinued the trial and 34 subjects completed the trial. 35 subjects were included in the full analysis set; all analyses were performed on the FAS. Since each subject received both treatments on 3 different treatment sites, the full analysis set comprised 105 test sites per treatment group. No major protocol deviations were observed during the trial.

The trial population comprised 25 (71.4%) men and 10 (28.6%) women. The mean age was 51.5 years; the mean duration of psoriasis was 24.0 years (range 2 to 53 years). Most subjects (88.6%) had Fitzpatrick skin type III.

Nearly equal proportions of subjects with 2 (16 [45.7%] subjects) and 3 target plaques (19 [54.3%] subjects) were observed.

The mean Baseline TCS was 6.6 both for test sites treated with LEO 90100 and test sites treated with Betesil® medicated plaster.
Efficacy Results

Primary Endpoint

LEO 90100 was more effective than Betesil® medicated plaster: a statistically significantly larger change in TCS from Baseline to end of treatment was found in the LEO 90100 group than in the Betesil® group (least squares mean difference -2.17; 95% CI -2.58 to -1.76; p<0.001)

Secondary Endpoints

A larger mean numeric change in TCS from Baseline was observed in the LEO 90100 group than in the Betesil® group from Day 8 to end of treatment.

A larger mean numeric change from Baseline in the score of each clinical sign (erythema, scaling, infiltration) was observed in the LEO 90100 group than in the Betesil® group from Day 8 to end of treatment.

A statistically significantly larger change in total skin thickness from Baseline to end of treatment was found in the LEO 90100 group than in the Betesil® group (least squares mean difference -0.42 mm; 95% CI -0.53 to -0.32; p<0.001)

A statistically significantly larger change in echo-poor band thickness from Baseline to end of treatment was found in the LEO 90100 group than in the Betesil® group (least squares mean difference -0.55 mm; 95% CI -0.69 to -0.41; p<0.001).

Safety Results

A total of 15 subjects (42.9%) experienced a total of 20 AEs after start of treatment with the 2 IMPs.

No deaths, other 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 AEs were headache (8 [22.9%] subjects), influenza (3 [8.6%] subjects) and oropharyngeal pain (3 [8.6%] subjects). All other AEs were reported by no more than 1 subject.

The majority of the AEs were mild, with 7 AEs in 7 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 showed that LEO 90100 was statistically significantly more effective after 4 weeks than Betesil® medicated plaster in subjects with psoriasis vulgaris.
**Electronic Signatures**

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