Clinical Study Report Synopsis

A vasoconstriction study with LEO 90100

A Phase 1 study comparing LEO 90100 aerosol foam, Dermovel®/Dermovate® cream, Daivobet® ointment, betamethasone dipropionate in the aerosol foam vehicle, Synalar® ointment and the aerosol foam vehicle

A phase 1 (pharmacodynamic) single centre, single application, randomised, investigator blinded study with intra-individual comparisons in healthy volunteers

LEO Pharma A/S
Clinical Development and Safety

Trial ID: LP0053-69
17-Feb-2014
EudraCT Number: 2012-002660-28
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:

[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:

[Signature]

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)

**Title of Trial:**
A Phase 1 study comparing LEO 90100 aerosol foam, Dermoval®/Dermovate® cream, Daivobet® ointment, betamethasone dipropionate in the aerosol foam vehicle, Synalar® ointment and the aerosol foam vehicle

**Investigators:**
The international coordinating investigator was [NAME], MD, Dermatologist, Centre de Pharmacologie Clinique Appliquée à la Dermatologie, Hôpital de l’Archet 2, 06202 Nice Cedex 3, France.

**Trial Centre:**
The trial was conducted at [ADDRESS], France.

**Publication(s) based on the trial:**
None at the time of this clinical study report.

**Trial Period:**
Date of first enrolment (informed consent signed and CRF started): 13-Sep-2013.
Date of last completed: 03-Oct-2013.

**Phase of Development:**
1

**Objectives:**
To compare the pharmacodynamic activity of LEO 90100 with Dermoval®/Dermovate® cream, Daivobet® ointment, betamethasone dipropionate in the aerosol foam vehicle, Synalar® ointment and the aerosol foam vehicle using the human skin blanching test (McKenzie-Stoughton's test).

**Methodology:**
Trial LP0053-69 was a single-centre, single application, randomised, investigator-blinded, active-, vehicle-controlled trial with intra-individual comparison in healthy subjects. Subjects who fulfilled all inclusion and exclusion criteria were planned to be randomised to receive topical administration of the following products:
- LEO 90100 aerosol foam (LEO 90100)
- Dermoval®/Dermovate® cream
- Daivobet® ointment
- Synalar® ointment
- Betamethasone dipropionate in the aerosol foam vehicle
- Aerosol foam vehicle (no-treatment control)

Seven circular sites (2.2 cm diameter) were outlined on the anterior face of each forearm. The products were applied according to random assignment on 6 test sites for 6 hours. One site was left untreated as a negative control. Visual estimation by trained observers of the degree of blanching were made prior to and at 7 time points up to 32 h after product application to obtain areas under the blanching curves and skin colour measurements using a chromameter. Local and systemic adverse events (AEs) were to be reported daily.

**Number of Subjects (Planned and Analyzed):**
Approximately 35 subjects were planned to be randomised in the trial to ensure 30 completed evaluable subjects. In total 35 subjects were randomised.
SYNOPSIS

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Diagnosis and Main Criteria for Inclusion:
The trial population was chosen with the intent to include healthy subjects, 18-50 years of age demonstrating adequate vasoconstriction to Daivobet® ointment within 15 days prior to dosing and to exclude those with skin conditions or use of medication that could have a potential impact on the trial results.

Investigational Products, 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
- Betamethasone dipropionate in the aerosol foam vehicle (betamethasone 0.5 mg/g, as dipropionate); Lot number: 123427401
- Aerosol foam vehicle (no active substance); Lot number: 123087102

Each subject received a single topical application of each product according to random assignment (see Methodology section above).

Duration of Treatment:
6 hours.

Reference Therapy, Dose and Mode of Administration, Batch Number:
- Dermoval®/Dermovate® cream (clobetasol propionate 0.05%); Lot number C590977
- Daivobet® ointment (calcipotriol 50 mcg/g and betamethasone 0.5 mg/g, as dipropionate); Lot number 120887101
- Synalar® ointment (fluocinolone acetonide 0.025%); Lot number N301A

Each subject received a single topical application of each product according to random assignment (see Methodology section above).

Criteria for Evaluation:
Pharmacodynamic Assessments:
Visual assessment of blanching was made subjectively by the two independent trained readers, at 6h10min, 8h, 10h, 12h, 24h, 28h and 32h after the product applications according to the following score: 0 = no change in skin colour; 1 = slight (barely visible) blanching; 2 = obvious blanching; 3 = intense blanching; 4= blanching judged to be maximal. At each evaluation time, two visual score values (one per trained evaluator) were recorded for each test site.
Colorimetric assessment was performed with a chromameter (Konica Minolta CR 400) at baseline (within 30 minutes prior to test product application (T0)) and 6h10min, 8h, 10h, 12h, 24h, 28h and 32h after the product applications (after visual assessments). By this colorimetric method colour is expressed in a three dimensional space. The L* value (luminance) gives the relative brightness and the a* value represents the balance between the red (positive values) and the green (negative values). The skin blanching effect will lead to an increase of the L* value and a decrease of the a* value compared to baseline. In the presented trial, two successive measures were performed on each test site at each time for each colorimetric parameter a* and L*. For analyses, the mean of the two values was used and the AUC0-32h was calculated.

Primary Response Criterion:
Visual assessment of skin blanching (visual score) expressed by the AUC0-32h by treatment site. The mean of visual assessments obtained at the same time points from 2 independent trained readers was used

Secondary Response Criteria:
- Skin colour measured by the chromameter:
  - Change from baseline in colorimetric parameter a* (the red/green balance) will be calculated at each time point (Δa*). AUC0-32h of this change by treatment site was calculated after subtraction of untreated site change
  - Change from baseline in colorimetric parameter L* (luminance) was calculated at each time point (ΔL*). AUC0-32h of this change by treatment site will be calculated after subtraction of untreated site change
**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)

Safety Assessments:
- Any AE reported
- Any adverse drug reaction reported
- Reason for withdrawal from the trial

Statistical Methods:
For all response criteria, the primary analyses were comparisons of LEO 90100 with Dermovate® cream, Daivobet® ointment, and Synalar® ointment

Primary response criterion
The AUC\(_{0-32h}\) of visual score was compared between treatment groups using an analysis of variance (ANOVA) with subjects, treatments, and site as factors. In case of significant treatment effect, estimates of treatment effect and 95% confidence interval of differences between treatment groups were calculated from the model without correction for multiplicity in the primary analysis. Correction for multiplicity using Tukey’s honestly significant difference method was used as secondary analysis.

Secondary response criteria
The change from baseline in colorimetric parameter a* (red/green balance) was calculated at each time point (Δa*). For each treatment site and time point the value of the change from baseline of the untreated site at the same time point was subtracted (ΔΔa*). The AUC\(_{0-32h}\) of this ΔΔa*was compared between treatment groups as described for the AUC\(_{0-32h}\) of visual score. Analyses of change from baseline in colorimetric parameter L* (luminance) were performed similarly.

**Summary of Results and Conclusions**

**Study Population:**
All 35 subjects randomised received a single application of each investigational product, attended all visits, and completed the trial.

Baseline demographics and subject characteristics for the 35 subjects were in line with the targeted trial population. All subjects were above 18 years of age and below 50 years of age (range: 21-49 years), no subjects had skin type V or VI (exclusion criterion No. 2), and the screening test for blanching response was in agreement with the required visual score of at least one unit (inclusion criterion No.3). No medical history or use of concomitant medications contradicted the eligibility requirements

Protocol deviations were considered as minor and no subjects were excluded from analysis sets due to protocol deviations.

**Summary of Pharmacodynamic Results:**

Primary Response Criterion - Visual Assessment of Skin Blanching
- All active products led to a skin blanching effect, as expressed by AUC\(_{0-32h}\) of visual assessment of skin blanching. Dermovate® cream showed the greatest degree of skin blanching (mean: 3,831), followed by BDP aerosol foam (mean: 2,595), LEO 90100 mean: 2,560), Daivobet® ointment (mean: 2,008), and Synalar® ointment (mean: 1,981).
- There was a significantly lower degree of skin blanching after treatment with LEO 90100 compared with the Dermovate® cream (p<0.001).
- There was a significantly greater degree of skin blanching after treatment with LEO 90100 compared with Daivobet® ointment (p=0.001).
- There was a significantly greater degree of skin blanching after treatment with LEO 90100 compared with the corticosteroid Synalar® ointment (p<0.001).
- There was no significant difference in degree of skin blanching between LEO 90100 and BDP aerosol foam.
- There was no significant difference in degree of skin blanching between Daivobet® ointment and Synalar® ointment.
**SYNOPSIS**
Name of Sponsor/Company: LEO Pharma A/S

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**Summary of Pharmacodynamic Results (continued):**
**Secondary Response Criterion - Change from Baseline in Colorimetric Parameter a* (The Red/Green Balance)**
- All active products led to a skin blanching effect, as assessed by the colorimetric parameter a* (the red/green balance). The numerical order of the degree of skin blanching among products was identical to that observed by visual assessments.
- There was a significantly lower degree of skin blanching after treatment with LEO 90100 compared with Dermovate® cream (p<0.001).
- There was no significant difference in degree of skin blanching between LEO 90100 and Daivobet® ointment.
- There was no significant difference in degree of skin blanching between LEO 90100 and Synalar® ointment.
- There was a significantly lower degree of skin blanching after treatment with LEO 90100 compared with BDP aerosol foam (p=0.020).
- There was no significant difference between Daivobet® ointment and Synalar® ointment.

**Secondary Response Criterion - Change from Baseline in Colorimetric Parameter L* (Luminance)**
- All active products led to a skin blanching effect, as assessed by the colorimetric parameter luminance. The numerical order of the degree of skin blanching among products was identical to that observed by visual assessments.
- There was a significantly lower skin blanching effect after treatment with LEO 90100 compared with Dermovate® cream (p<0.001).
- There was a significantly greater skin blanching effect after treatment with LEO 90100 compared with Daivobet® ointment (p=0.048).
- There was significantly greater skin blanching effect after treatment with LEO 90100 compared with Synalar® ointment (p=0.023).
- There was no significant difference in skin blanching between LEO 90100 and BDP aerosol foam.
- There was no significant difference in skin blanching between Daivobet® ointment and Synalar® ointment.

**Summary of Safety Results:**
- No subjects experienced AEs in the trial.
- LEO 90100 was well tolerated.

**Conclusion:**
- LEO 90100 showed a substantially lower skin blanching effect than Dermovate® cream but higher than Daivobet® ointment and Synalar® ointment.
- The results indicate that the corticosteroid potency of LEO 90100 is closer to Daivobet® ointment and the mid potency corticosteroid Synalar® ointment than to the super potent corticosteroid Dermovate® cream.
LP0053-69 Clinical Study Report Synopsis EudraCT no. 2012-002660-28 17-Feb-2014 - English

**ELECTRONIC SIGNATURES**

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