Clinical Study Report Synopsis

Combined Cumulative Irritation Potential and Repeat Insult Patch Test of LEO 90100 Aerosol Foam

A phase 1 study evaluating the skin irritation potential and sensitisation potential of LEO 90100 aerosol foam and the aerosol foam vehicle after repeated applications to the skin of healthy subjects

A single-centre, prospective, randomised, investigator-blinded, vehicle- and negative-controlled clinical study, with intra-individual comparison of treatments

LEO Pharma A/S
Clinical Development and Safety

LP0053-66
18-Jun-2014
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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:

[Name], MD
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 evaluating the skin irritation potential and sensitisation potential of LEO 90100 aerosol foam and the aerosol foam vehicle after repeated applications to the skin of healthy subjects

Investigator:
The international coordinating investigator was [Redacted], MD, 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 [Redacted], 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): 02-Sep-2013
Date of last completed: 06-Dec-2013

Objectives:
The primary objective of the trial was to determine the skin irritation potential and sensitisation potential of LEO 90100 aerosol foam and the aerosol foam vehicle after repeated applications on the skin of healthy subjects.

Methodology:
Trial LP0053-66 was a single-centre, prospective, randomised, investigator-blinded, vehicle- and negative controlled phase 1 trial with intra-individual comparison in healthy subjects. Subjects who fulfilled all eligibility criteria were randomised to receive repeated topical applications of each of the following products:
- LEO 90100 aerosol foam (LEO 90100)
- Aerosol foam vehicle
- Vaseline officinale Cooper (white petrolatum; negative control)

The trial consisted of 4 phases: a screening phase (up to 6 weeks), an induction phase (3 weeks), a rest phase (2 weeks), and a challenge phase (5 or 6 days)

During the 21-day *induction phase*, each subject received 15 applications on small test areas (4 cm²) on the skin of each investigational product distributed as 5 applications per week (every day except weekends). Throughout the induction phase, each investigational product was applied on the same test site on the subject’s middle back under semi-occlusive conditions. The dermal response was scored using a 6-point standardised visual assessment scale (0, 0.5, 1, 2, 3, and 4) 30 minutes after removal of each semi-occlusive patch and if applicable, gently removal of excess product on the skin.

The *challenge phase* (Day 36 to Day 40) was initiated after the 2 weeks’ rest phase by applying each investigational product on a treatment-naive skin test site on the subject’s upper back under semi-occlusive conditions. The dermal response was scored using a 6-point standardised visual assessment scale 30 minutes, 24, and 48 hours (potentially at 72 hours at the investigator’s discretion) after removal of each semi-occlusive patch and if applicable, gently removal of excess product on the skin.

All applications were performed by designated trial personnel at the trial site.

Concomitant medication and AEs were reported throughout the trial.
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Number of Subjects (Planned and Analysed):
Approximately 220 subjects were planned to be randomised in the trial to ensure 200 completed evaluable subjects. In total, 218 subjects were randomised.

Diagnosis and Main Criteria for Inclusion:
The trial population was chosen with the intent to include healthy subjects, 18-65 years of age and to exclude those with skin conditions or use of medication that could have a potential impact on the trial results.

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
Each subject received repeated topical applications according to random assignment (see Methodology section above). In total, each subject received approximately 122 mg × 16 times of the aerosol foam product, corresponding to 50 mg per dose after evaporation of the propellants.

Duration of Treatment:
Each subject received 15 applications during the induction phase (Day 1- Day 21) and 1 application in the challenge phase (Day 36 to Day 40).

Reference Therapy, Dose and Mode of Administration, Batch Number:
- Aerosol foam vehicle; Lot number: 123087102
- Vaseline officinale Cooper (white petrolatum; negative control); 12110078D
Each subject received repeated topical applications according to random assignment (see Methodology section above). In total, each subject received approximately 122 mg × 16 times of the aerosol foam product, corresponding to 50 mg per dose after evaporation of the propellants and 50 mcl × 16 times of the negative control.

Criteria for Evaluation:
Safety:
The primary response criteria were:
- Skin irritation potential:
  Mean Cumulative Irritation Index (MCII) and maximal dermal response during the induction phase (Day 2-22) were considered as co-primary endpoints for skin irritation potential assessments
- Skin sensitisation potential:
  Number of subjects with positive sensitisation according to investigator’s assessment of sensitisation at the end of the challenge phase

Note: The induction phase took place from Day 1 to Day 21 and the patch after the last application was removed on Day 22. Thus the final test site assessment pertaining to the induction phase was made on Day 22.

The secondary response criterion was:
- Dermal response by visit during induction and challenge phase and maximal dermal response during the challenge phase

Other safety criteria:
- Any adverse event reported
- Any adverse drug reaction (ADR) reported
- The reason for withdrawal from the trial
SYNOPSIS
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Statistical Methods:
Skin irritation potential:
Based on the visual scorings during the induction phase (dermal response), a Cumulative Irritancy Index (CII) for each subject was calculated for each product as CII = Sum of clinical scores across readings (Day 2-22)/number of readings. The MCII was calculated for each treatment group by averaging individual CIIs across subjects. MCII and its 95% confidence interval (CI) were tabulated per treatment group. MCII of aerosol foam investigational products were compared with the negative control using a two-way analysis of variance (ANOVA) having subjects and treatments as factors. Treatment differences were tested as contrasts and 95% CI of differences between aerosol foam investigational products and the negative control were calculated. Maximal dermal response (analysed as a quantitative parameter) observed during the induction phase was analysed as described above for MCII.

Skin sensitisation potential:
The count and frequency of subjects by category of dermal response and the maximum dermal response observed during the challenge phase were tabulated by time and treatment group.

Summary of Results and Conclusions
Study Population:
In total, 224 subjects were screened and 218 subjects were randomised and received at least one application of investigational product. In total, 4 of the randomised subjects withdrew from the trial and 214 (98%) subjects completed the trial. Important protocol deviations were identified for 5 subjects and their data were therefore excluded from the analysis sets defined for evaluation of the skin irritation potential and the skin sensitisation potential. Both analysis sets thus comprised the same 213 subjects. Among the 218 randomised subjects, one subject was lost to follow-up after first application and did not provide post-randomisation data and was excluded from the safety analysis set. The safety analysis set thus comprised 217 subjects.

Overall, baseline demographics and subject characteristics for the 213 subjects were in line with the targeted trial population. All subjects were above 18 years of age and below 66 years of age (range: 19-65 years), and no subjects had skin type V or VI (exclusion criterion No. 3). The outcome of physical examinations at baseline was normal for all subjects and all subjects had baseline skin assessments of dermal response evaluated as ‘no response’. No medical history contradicted the eligibility requirements.

Summary of Safety Results:
Skin Irritation Potential
- During the induction phase (Day 1 to 21), the majority of subjects had a maximum dermal response score of 0 (‘no response’) or 0.5 (‘questionable or faint, indistinct erythema’), reported for 168 (78.9%) subjects after application of LEO 90100 and 209 (98.1%) subjects after application of both the aerosol foam vehicle and the negative control. A maximum dermal response score of 1 (‘well-defined erythema’) was reported for 42 (19.7%) subjects after application of LEO 90100 and for 4 (1.9%) after application of both the aerosol foam vehicle and the negative control.
- The highest reported dermal response score was 2 (‘erythema with slight to moderate oedema’), reported in 3 (1.4%) subjects after application of LEO 90100.
- The mean maximal dermal response during the induction phase (co-primary endpoint) was 0.44 for LEO 90100, 0.16 for the aerosol foam vehicle, and 0.13 for the negative control (white petrolatum). There was a statistically significant difference between LEO 90100 and the negative control (95% CI 0.25 to 0.37; p<0.001). The maximal dermal response for the aerosol foam vehicle was similar to the negative control.
- The MCII during the induction phase (co-primary endpoint) was low for all treatments; 0.102 for LEO 90100, 0.019 for the aerosol foam vehicle, and 0.018 for the negative control (white petrolatum). There was a statistically significant difference between LEO 90100 and the negative control (95% CI 0.069 to 0.101; p<0.001). The MCII for the aerosol foam vehicle was similar to the negative control.
### SYNOPSIS

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### Summary of Safety Results (continued):

#### Skin Sensitisation Potential

- During the challenge phase (Day 36 to Day 40), the majority of subjects had a maximum dermal response score of 'no reaction'. A maximum dermal response score of ‘doubtful reaction (faint erythema only)’, was reported for 52 (24.4%) subjects after application of LEO 90100, for 2 (0.9%) after application of the aerosol foam vehicle, and for 4 (1.9%) subjects after application of the negative control. The highest reported dermal response score was 'weak positive reaction (erythema infiltration, possibly papules)', reported in 2 (0.9%) subjects after application of LEO 90100.

- During the challenge phase, the majority of those reactions evaluated as either 'doubtful reactions' or 'weak positive reactions' were observed on Day 38 (start of challenge phase) for all treatment groups, and the frequency of these reactions decreased successively during the challenge phase. On Day 40, 6 (2.8%) subjects in the LEO 90100 group had a 'doubtful reaction' whilst all other subjects, including the aerosol foam vehicle- and the negative control groups, had 'no reaction'.

- Taking into account the dermal response evaluations performed in the challenge phase, the investigator concluded that there was no indication of a sensitisation reaction for any subject.

#### Adverse Events

- In total, 116 AEs were reported. There were no deaths in the trial. One SAE was reported and led to withdrawal from the trial. The SAE was assessed as having no relation to investigational product. No other AEs led to discontinuation from treatment or trial. The vast majority of the AEs were mild or moderate and only 3 AEs were rated as severe.

- The overall incidence of AEs was 86 (39.6%) subjects reporting 116 AEs. The most frequently reported AEs were nasopharyngitis and folliculitis, both reported by 20 (9.2%) subjects and headache, reported by 27 subjects (12.4%).

- In total, 31 AEs were localised on the application areas and consisted of 20 events of folliculitis, 8 events of pruritus, 2 events of urticaria, and 1 event of skin irritation. All events were non-serious and the majority of events (29 of 31) were reported after application of LEO 90100. The 2 other events (urticaria and skin irritation) were reported after application of the aerosol foam vehicle. The vast majority of AEs on the application areas were mild (19 events) or moderate (11 events) in intensity. One AE was evaluated as severe and concerned folliculitis reported after application of LEO 90100. The reported outcome was 'recovered'.

#### Conclusion:

- LEO 90100 had a low skin irritation potential in healthy subjects. The aerosol foam vehicle alone was shown to be non-irritant.

- LEO 90100 as well as the aerosol foam vehicle alone showed no skin sensitisation potential in healthy subjects.

- There were no unexpected AEs.