Clinical Study Report Synopsis

Efficacy and safety of LEO 80185 gel (calcipotriol hydrate plus betamethasone dipropionate) in Japanese subjects with psoriasis vulgaris

Design of trial:

A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 80185 gel versus Dovobet® ointment (each containing calcipotriol hydrate 52.2 μg/g [equivalent to 50.0 μg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g)

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: LP0076-1128
Date: 22-Nov-2016
Version: 1.0
Clinical Study 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:

PPD, MSc
Biostatistics Lead, Global Clinical Operations

PPD, MD
Medical Lead, Medical Sciences and Safety

Approval Statement, International Coordinating Investigator

The international 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:

Professor Hidemi Nakagawa, MD, PhD
International coordinating investigator
Trial Registration Number
NCT 02668692

EudraCT number
N/A

Title of Trial
Efficacy and safety of LEO 80185 gel (calcipotriol hydrate plus betamethasone dipropionate) in Japanese subjects with psoriasis vulgaris

Investigators
Professor Hidemi Nakagawa, MD, PhD, Chairman and Professor, Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan was appointed as signatory investigator.

Trial Centres
This trial was conducted at 27 centres in Japan.

Publications
None at the time of the final clinical trial report.

Clinical Trial Period
Date of First Subject First Visit: 04-Feb-2016
Date of Last Subject Last Visit: 25-Jun-2016

Development Phase
Phase 3

Objectives
Primary Objective
To compare the efficacy of LEO 80185 gel with Dovobet® ointment in the treatment of scalp psoriasis in Japanese subjects.

Secondary Objectives
To compare the efficacy of LEO 80185 gel with Dovobet® ointment in the treatment of psoriasis on non-scalp areas of the body in Japanese subjects.
To compare the safety of LEO 80185 gel with Dovobet® ointment in the treatment of psoriasis on the scalp and non-scalp areas of the body in Japanese subjects.

Methodology
This was a phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 80185 gel versus Dovobet® ointment in Japanese subjects with psoriasis vulgaris.

Number of Subjects Planned and Analysed
200 subjects were planned and 206 subjects were randomised to treatment and analysed.

Diagnosis and Main Criteria for Inclusion
1. Japanese subjects aged 20 years or above
2. Clinical diagnosis of psoriasis vulgaris amenable to topical treatment of less than or equal to 30% body surface area (excluding any psoriasis on the face/genitals/skin folds)
3. A target psoriasis lesion on the scalp and non-scalp area of body, each lesion of a minimum size of 10 cm² and scoring at least 2 (mild) for each of redness, thickness and scaliness
4. Females of childbearing potential must have a negative result for a urine pregnancy test and must agree to use an adequate method of birth control

Test Product, Dose and Mode of Administration, Batch Number
LEO 80185 gel (containing calcipotriol hydrate 52.2 μg/g [equivalent to 50.0 μg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) applied to target lesions and any other areas of psoriasis (except any on the face/skin folds/genitals) once daily. Batch number P 15035.

Duration of Treatment
Screening period: up to 4 weeks
Treatment period: 4 weeks
Follow-up period (if required): up to 2 weeks

Reference Product, Dose and Mode of Administration, Batch Number
Dovobet® ointment (containing calcipotriol hydrate 52.2 μg/g [equivalent to 50.0 μg/g calcipotriol] plus betamethasone dipropionate 0.643 mg/g) applied to target lesions and any other areas of psoriasis (except any on the face/skin folds/genitals) once daily. Batch number P 15034.
Criteria for Evaluation
Each target lesion (on scalp and non-scalp area) was assessed for severity of redness, thickness and scaliness (each on a scale of 0 = none to 4 = severe) and the general change from baseline (markedly improved, moderately improved, slightly improved, unchanged, aggravated). Subjects assessed ease of application (very easy, easy, difficult, very difficult) and stickiness of the medication (not sticky, slightly sticky, moderately sticky, very sticky).

Adverse events were collected at all visits and evaluated for severity (mild, moderate, severe) and causal relationship to trial medication. Other significant AEs (besides deaths and SAEs) were identified at the data review meeting at the end of the trial. Blood and urine samples were taken at the start and end of the trial and analysed for haematology/chemistry and urine glucose/protein, respectively.

Primary Endpoint
‘Overall improvement’ for the target lesion on the scalp at Visit 4 (end of Week 4), defined as ‘substantial resolution’ of clinical signs and/or at least ‘moderately improved’ in the general change in the lesion. ‘Substantial resolution’ was defined as a score for thickness and scaliness of 0 and a score for redness of 1 or less.

Secondary Endpoints
‘Overall improvement’ for the target lesion on non-scalp area of body at Visit 4 (end of Week 4) defined as ‘substantial resolution’ of clinical signs and/or at least ‘moderately improved’ in the general change in the lesion. ‘Substantial resolution’ was defined as a score for thickness and scaliness of 0 and a score for redness of 1 or less.

The change in the sum of the scores (total sign score) for the severity of redness, thickness and scaliness from baseline to Visit 4 (end of Week 4) for each target lesion.

Statistical Methods
Efficacy
All significance tests were two-sided using the 5% significance level. Analysis of efficacy endpoints used the per protocol analysis set (PPAS) as the primary analysis.

The proportion of subjects with ‘overall improvement’ for each target lesion at Visit 4 was compared between treatment groups by means of Fisher’s exact test. Estimated rates, the odds ratio, its 95% confidence interval and p-value from the Fisher’s exact test are presented.

The difference (LEO 80185 gel group – Dovobet® ointment group) in the proportion of subjects with ‘overall improvement’ and its 95% confidence interval are also presented for the primary endpoint.

Descriptive statistics (mean, SD, median, minimum, maximum) are presented for the change from baseline to Visit 4 for the total sign score for each target lesion for each group.

Summary of Results
Trial Population
In total, 206 subjects (101 in the LEO 80185 group and 105 in the Dovobet® group) were randomised and treated with at least one application of the trial medication, and 205 subjects (100 in the LEO 80185 group and 105 in the Dovobet® group) completed the trial. Of the 206 subjects randomised, all were included in the full analysis set (FAS) and safety analysis set and 12 (7 in the LEO 80185 group, 5 in the Dovobet® group) were excluded from the PPAS, mainly due to use of prohibited concomitant medication.

In the LEO 80185 group, 66.3% were men, mean age was 51.0 years, and mean total sign score at baseline was 8.05 for the target lesion on the scalp and 8.31 for the target lesion on non-scalp area. Corresponding figures for the Dovobet® group were 80.0%, 54.3 years, 8.22 and 8.40. The compliance with the use of the trial medication was good, and more than 90% of subjects in both groups had no missed application.
Efficacy Results

The number of subjects with 'overall improvement' on the scalp at Visit 4 was 92 (97.9%) in the LEO 80185 group and 96 (96.0%) in the Dovobet® group. The odds ratio was 1.92 (95% CI: 0.34 to 10.72; P=0.68). Therefore no statistically significant difference was found between the two groups. The difference (LEO 80185 group –Dovobet® group) in the proportion of subjects with 'overall improvement' was 1.87% (95% CI: −2.95% to 6.70%). Therefore no statistically significant difference was found between the two groups.

The number of subjects with 'overall improvement' on the non-scalp area was 76 (80.9%) in the LEO 80185 group and 95 (95.0%) in the Dovobet® group. The odds ratio was 0.22 (95% CI: 0.08 to 0.63; P=0.003). Therefore a statistically significant difference was found between the two groups.

Subjects with 'overall improvement' for the target lesions at Visit 4 (Week 4 - LOCF): PPAS

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<th>Non-scalp area</th>
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<tbody>
<tr>
<td></td>
<td>LEO 80185 gel</td>
<td>LEO 80185 ointment</td>
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<tr>
<td>Overall improvement</td>
<td>(n=94) N (%)</td>
<td>(n=100) N (%)</td>
</tr>
<tr>
<td></td>
<td>92 (97.9)</td>
<td>96 (96.0)</td>
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<tr>
<td>Not overall improvement</td>
<td>2 (2.1)</td>
<td>4 (4.0)</td>
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Odds ratio\(^1\) 1.92 0.22
95% CI of odds ratio [0.34, 10.72] [0.08, 0.63]
P-value\(^2\) P=0.68 P=0.003
Difference (%)\(^3\) 1.87 -
95% CI of difference [-2.95, 6.70] -

[1] Odds of ‘overall improvement’ in LEO 80185 gel group relative to Dovobet® ointment group.
[3] Difference in % of subjects with overall improvement (LEO 80185 gel group - Dovobet® ointment group)

Mean change in total sign score on the scalp from baseline to Visit 4 was −6.43 in the LEO 80185 group and −6.79 in the Dovobet® group. There was no statistically significant difference between the two groups.

Mean change in total sign score on the non-scalp area from baseline to Visit 4 was −5.31 in the LEO 80185 group and −6.46 in the Dovobet® group. The Dovobet® group therefore showed a greater decrease.

The proportions of subjects who assessed the ease of application as ‘very easy’ and stickiness as ‘not sticky’ were higher in the LEO 80185 group than the Dovobet® group on both scalp and non-scalp areas; ‘very easy’ on the scalp (39.4% in the LEO 80185 group, 6.0% in the Dovobet® group) and non-scalp area (60.6%, 32.0%), and ‘not sticky’ on the scalp (34.0%, 4.0%) and non-scalp area (59.6%, 26.0%).

Safety Results

Adverse events occurred in 13 subjects (12.9%) in the LEO 80185 group and in 9 subjects (8.6%) in the Dovobet® group. None of the events were severe. The incidence of lesional/perilesional AEs was low in both groups; 3.0% in the LEO 80185 group and 1.0% in the Dovobet® group, and all were mild. The proportion of subjects with AEs related to the trial medication was 5.9% in the LEO 80185 group and 1.9% in the Dovobet® group, and all were mild.

One SAE (meningitis) occurred in 1 (1.0%) subject in the LEO 80185 group. The subject withdrew from the trial due to the event. The event was considered not related to the trial medication. No other SAEs or AEs leading to withdrawal were reported. No deaths were reported.

Other significant AEs occurred in 6 subjects (5.9%) in the LEO 80185 group and in 2 subjects (1.9%) in the Dovobet® group, and all were mild.

Mean changes in laboratory values during the trial were small.

Conclusion

Both LEO 80185 gel and Dovobet® ointment had a similarly high response rate in scalp psoriasis in Japanese subjects. The LEO 80185 gel demonstrated a high response rate in non-scalp psoriasis, though Dovobet® ointment had a higher response.


The data suggest that subjects find LEO 80185 gel easier to apply and less sticky than Dovobet® ointment.

In conclusion, LEO 80185 gel is considered a useful alternative dosage form of Dovobet® ointment.
ELECTRONIC SIGNATURES

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