SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S

Location of study report in Regulatory Dossier for authorities

Name of Investigational Product/Finished Product, if available: DAIVOBET/DOVOBET gel (LEO 80185)

Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Title of study/Protocol Code Number: Assessment of the Atrophogenic Potential and Dermal Tolerance of DAIVOBET/DOVOBET Gel Compared with Diprosone® Ointment MBL 0601 FR.

Centre details:
Single centre located in France

Publication references:
To be decided.

Study period details:
Date of first subject enrolment 03-May-2006, and date of last subject completed 26-Jun-2006.

Phase of development:
I

Objectives/hypothesis, if applicable:
The objective of this study was to investigate if the atrophogenic potential of DAIVOBET/DOVOBET gel containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) was less than or equal to the skin thinning produced by Diprosone® ointment containing betamethasone 0.5 mg/g (as dipropionate) alone. In addition, the dermal tolerance of DAIVOBET/DOVOBET gel compared with Diprosone® was evaluated.

Study methodology:
Single centre, prospective, randomised, active and vehicle controlled, partly blinded, right/left comparison within the two treatment groups, 4-week treatment study in healthy subjects.

The subjects were randomly assigned to one of two groups, A or B: - in Group A (32 subjects), a right/left comparison was made between DAIVOBET/DOVOBET gel and Diprosone® ointment
- in Group B (16 subjects), a right/left comparison was made between DAIVOBET/DOVOBET gel and the gel vehicle.

Treatments were applied once daily to test fields on the right and left forearms according to randomisation.

Each subject was supplied with the two treatments, one for the left arm and one for the right arm. The dispensed treatments were applied topically, once daily for 4 weeks (28 days) to test fields measuring approximately 5 x 6 cm on the right and left volar forearm according to instructions given to the subject at the beginning of the study. The test fields were specified at Visit 1.

**Sonography**

Sonographic measurements to assess skin thickness were performed by a technician on the test sites on Days 0, 7, 14, 21, 28 and 42.

Sonographic measurements were performed using Dermascan C 20 MHz (software version 1.6.2.5.2, manufactured by CORTEX, Hadsund, Denmark).

**Assessment of skin atrophy, teleangiectasia and erythema**

Clinical assessment of skin atrophy, teleangiectasia and erythema was performed in terms of visual inspection by a dermatologist on Days 0, 7, 14, 21, 28 and 42 according to scales ranging from 0 to 4.

**Number of patients enrolled:**

53 subjects were enrolled and 48 subjects were randomised (32 in Group A and 16 in Group B).

**Diagnosis and main criteria for patient selection:**

The subjects to be included in this study should had been healthy as defined by medical history and a physical examination (including a urine pregnancy test for the females) made
Subjects were to be 18 to 50 years old and had to give written informed consent.

Investigational product, dose, method of administration, batch numbers:

<table>
<thead>
<tr>
<th>Product name</th>
<th>DAIVOBET/DOVOBET gel (calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g as dipropionate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unit dose</td>
<td>Approximately 60 mg gel per application</td>
</tr>
<tr>
<td>Regimen</td>
<td>Twenty-eight (28) applications in total</td>
</tr>
<tr>
<td>Mode/Route</td>
<td>Topical</td>
</tr>
<tr>
<td>Batch number</td>
<td>04 219 61 01/08 2006</td>
</tr>
</tbody>
</table>

Reference product, dose, method of administration, batch numbers:

<table>
<thead>
<tr>
<th>Product name</th>
<th>Betamethasone 0.5 mg/g (as dipropionate) ointment (Diprosone®)</th>
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</thead>
<tbody>
<tr>
<td>Unit dose</td>
<td>Approximately 60 mg ointment per application</td>
</tr>
<tr>
<td>Regimen</td>
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<table>
<thead>
<tr>
<th>Product name</th>
<th>Gel vehicle</th>
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<tbody>
<tr>
<td>Unit dose</td>
<td>Approximately 60 mg gel per application</td>
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Duration of treatment:
The study included a screening phase (2 weeks), a treatment phase (4 weeks) and a treatment-free-phase with final visit (2 weeks).

Criteria for evaluation
Sonography and Clinical Assessments:
- **Primary response criterion:** Percentage change in skin thickness from baseline to Day 28.
- **Secondary response criteria:** Absolute change in skin thickness from baseline to Day 28. Clinical scores for skin atrophy, teleangiectasia and erythema.

Evaluation of Adverse Events:
- Any reported adverse events.
- Any reported adverse drug reactions.
- Reasons for withdrawal from the study.

Statistical methodology:
For change and percentage change in skin thickness from baseline to Day 28, a point estimate and a 95% confidence interval were calculated by treatment. Similarly, a point estimate and a 95% confidence interval for the difference at Day 28 between the treatments were calculated.

Summary – Conclusions
Sonography results:
For treatment Group A (DAIVOBET/DOVOBET gel compared to Diprosone® ointment), the decrease in skin thickness on the arm applied with DAIVOBET/DOVOBET gel was comparable to that on the arm applied with Diprosone® ointment and corresponded to a maximum mean decrease of 10.64% (reported at Visit 5, Day 28) – compared to 11.10% for Diprosone®. The mean difference was 0.5 percentage points (95% confidence interval [CI] -2.4 to 3.3). Thus, there was no statistically significant difference in skin thinning between Daivobet® gel and Diprosone® ointment.

For both products, the skin thinning was reversible after the end of treatment.
<table>
<thead>
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<th>Name of Sponsor/Manufacturer</th>
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<th>(For National Authority Use only)</th>
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<td>Name of Active Substance</td>
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<tr>
<td>Calcipotriol plus betamethasone dipropionate</td>
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For treatment Group B (DAIVOBET/DOVOBET gel compared to gel vehicle), the decrease in skin thickness on the arm applied with DAIVOBET/DOVOBET gel corresponded to a maximum mean decrease of 7.85% (reported at Visit 5, Day 28). The skin thinning was reversible after the end of treatment. There was no apparent skin thinning effect of the gel vehicle.

The mean difference was -6.6 percentage points (95% CI -11.5 to -1.8). Thus, a statistically significant skin thinning effect was observed for Daivobet® gel compared with the gel vehicle. This effect was reversible after end of treatment.

Clinical Assessments:
The scores for skin atrophy, teleangietasia and erythema were 0 for all subjects at all visits during the study.

Adverse Events:
No serious adverse events were reported and no subject was discontinued from the study for reasons related to the study treatment.
No adverse events were reported on the application site.
During the study, 5 subjects reported a total of 7 non-cutaneous adverse events, none of which were considered as not related to the study treatment.

Conclusion:
A skin thinning effect of the order of 10% from baseline to Day 28 was observed for DAIVOBET/DOVOBET gel, which was reversible after end of treatment. The skin thinning effect observed for DAIVOBET/DOVOBET gel was similar to the one induced by Diprosone® ointment. No statistically significant difference was seen between the two products in this respect. A confidence interval indicated the difference most likely is less than 4 percentage points.
The skin thinning effect observed for DAIVOBET/DOVOBET gel was statistically significant compared to the gel vehicle for which no skin thinning was observed. This indicates that the results obtained from this model can be considered valid. No clinical signs of atrophy were observed in any of the subjects, and repeated application of 60 mg DAIVOBET/DOVOBET gel was safe and well tolerated.