SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S

Name of Finished Product: DAIVOBET/DOVOBET gel

Name of Active Ingredient: Calcipotriol + Betamethasone dipropionate

Title of trial: Effect of LEO 80185 Gel on the HPA axis and Calcium Metabolism in Subjects with Extensive Psoriasis Vulgaris

Trial centre(s): 10 dermatology centres in Canada.

Publication (reference): Not applicable

Trial period (years) 2010 - 2011
Date of first enrolment 13-NOV-2010
Date of last completed 06-SEP-2011

Phase of development: Phase 2

Objectives:
Primary: To evaluate the effect of once daily use of DAIVOBET/DOVOBET gel on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism in subjects with extensive psoriasis vulgaris.
Secondary: To evaluate other safety aspects, efficacy, and the pharmacokinetic profile of DAIVOBET/DOVOBET gel following topical application under maximal use conditions.

Methodology:
A national, multicentre, prospective, non-controlled open, single-group, 8-week study in subjects with extensive psoriasis vulgaris. Subjects received once-daily topical treatment with DAIVOBET/DOVOBET gel on all lesions on the scalp, trunk and/or limbs (excluding genitals and skin folds) for up to 8 weeks. Screening visits were performed at Day-56 to -7 (SV1), and between Day -7 and Day-3 (SV2). Treatment start was Day 0 (Visit 1). On-treatment visits were Days 14, 28, 42 and 56 (Visits 2, 3, 4, and 5). A 24-hour urine collection for assessment of calcium was taken on Days -7 to -3, 28 and 56 (Visits SV2, 3 and 5). An adrenocorticotropic hormone (ACTH) challenge test for assessment of adrenal function was performed at 8 a.m. ± 30 minutes between Days -7 to -3, on Days 28 and 56 (Visits SV2, 3 and 5). A follow-up visit took place 14 days after the patient’s last study visit if a safety follow-up (for any adverse event (AE) classified as possibly/probably related or not assessable relationship to treatment or for a clinically significant laboratory abnormality) was required. If HPA axis suppression was noted at Visits 3 or 5 a follow-up ACTH challenge retest took place 28 days after the visit. DAIVOBET/DOVOBET gel was applied to lesions on the scalp and the body once daily starting on Day 0 (Visit 1). Subjects whose psoriatic lesions had cleared after 4 weeks (Visit 3) left the study; subjects who had psoriatic lesions after 4 weeks continued once daily treatment for another 4 weeks. A complete physical examination (including vital signs), routine blood and urine laboratory tests were conducted at Day -7 to -3 (SV2), Day 28 (Visit 3) and Day 56 (Visit 5). Blood samples for pharmacokinetic assessment of calcipotriol, betamethasone and their two metabolites (MC1080 and betamethasone 17- propionate) were taken on Days -7 to -3 and 28 (Visits SV2 and 3) before application of study medication and at Visit 3 after 1, 2, 3, 5, and 7 hours. Adverse events were recorded at all visits except Day -56 to -7 (SV1). Psoriasis on the body was assessed by the investigator’s global assessment of disease severity (IGA) at all visits except Day -56 to -7 (SV1) and the follow-up visits.
Diagnosis and main criteria for inclusion:
Subjects of either sex, aged 18 years or above with psoriasis vulgaris involving trunk and/or limbs with or without scalp involvement amenable to topical treatment with a maximum of 100 g of study medication per week, with a total extent on scalp and trunk/limbs of 15-30% of body surface area (BSA) excluding face, genitals and skin folds. Disease severity on the trunk/limbs graded as at least moderate according to the IGA. Normal HPA axis function at baseline and albumin corrected serum calcium below the upper limit of the reference range.

Test product, dose and mode of administration, batch number:
DAIVOBET/DOVOBET gel containing calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate) applied topically once daily to psoriasis lesions on scalp, trunk, arms and legs up to maximum 100 g gel per week. Batch number 101767201

Duration of treatment:
4 or 8 weeks.

Reference therapy, dose and mode of administration, batch number:
Not applicable

Criteria for evaluation:
Safety:
Primary endpoint: the adrenal response to ACTH stimulation test defined as serum cortisol concentration obtained after 30 minutes at Day 28 and Day 56. Also the change in albumin-corrected serum calcium, 24-hour urinary calcium excretion and urinary calcium:creatinine ratio from baseline SV2 to Days 28 (Visit 3) and 56 (Visit 5).
Secondary endpoints were: subjects with serum cortisol ≤18 mcg/dL at 30 and 60 minutes after ACTH-challenge at Days 28 and 56 (Visits 3 and 5), adverse drug reactions (ADRs), AEs, change from baseline (Visit SV2) to Day 28 (Visit 3) and Day 56 (Visit 5) in serum phosphate, 24-hour urinary phosphate excretion, urinary phosphate:creatinine ratio, 24-hour urinary hydroxyproline excretion, urinary hydroxyproline:creatinine ratio, urinary sodium:creatinine ratio, serum alkaline phosphatase, plasma parathyroid hormone, other laboratory parameters, blood pressure, heart rate and reasons for withdrawal from the study.

Efficacy:
Subjects with “controlled disease” (“clear” or “almost clear”) according to the IGA at Day 28 and Day 56.

Pharmacokinetics:
Area under the curve to last measurable concentration (AUC0-t), area under the curve to infinity (AUC0-∞), maximum plasma concentration (Cmax), Time to maximum plasma concentration (tmax) and apparent elimination half life (t½) for calcipotriol, betamethasone dipropionate, MC1080 and betamethasone 17-propionate.

Statistical methods:
The analysis of the ACTH challenge test was based on the per-protocol analysis set (n=43), AE and laboratory data were analysed using the safety analysis set (n=43) and the efficacy analysis was based on the full analysis set (n=43). The change in albumin-corrected serum calcium, 24-hour urinary calcium excretion and urinary calcium:creatinine ratio from baseline (SV2) to Days 28 and 56 (Visits 3 and 5) was calculated. For treatment-emergent AEs the number of subjects experiencing each AE (preferred term) and the percentage of subjects with AEs was tabulated. Laboratory values and vital signs were listed, flagged for values outside the reference ranges and summarised by visit where appropriate for observed
values and changes from baseline (SV2). The frequency of subjects who achieved “controlled disease” according to the IGA was calculated. The pharmacokinetic parameters (AUC_{0-t}, AUC_{0-\infty}, C_{\text{max}}, t_{\text{max}} \text{ and } t_{\frac{1}{2}}) were estimated where scientifically valid and summary statistics given as appropriate for each compound.

### SUMMARY - CONCLUSIONS

#### RESULTS:

**Adrenal function:** Three (7.0%) subjects had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28. None of the 36 subjects who continued to Day 56 had a 30 minute serum cortisol ≤18 mcg/dL. Of the three subjects who had a serum cortisol value of ≤18 mcg/dL 30 minutes after the ACTH challenge test at Day 28, two were considered to show signs of adrenal suppression. The adrenal suppression was considered borderline in one of these subjects because the 30 minute value was only slightly below the defined cut off level. In this subject the 60 minute value showed adequate response and, in addition, the pre-test serum cortisol level was above the lower limit of the reference range. One subject showed clear signs of adrenal suppression with a cortisol level considerably lower than the cut off level at 30 minutes. In this subject the 60 minutes value was below the cut off level as well and also the pre-test level was below the lower limit of the reference range. Betamethasone 17-propionate was detectable in the pharmacokinetic (PK) samples for this subject. This subject also showed signs of a possibly clinically relevant increase in 24-hour urinary excretion but calcipotriol and its main metabolite were below the lower limit of quantification (LLOQ) in the PK samples. The third subject was not considered to show adrenal suppression because the pre-test cortisol value was 21.2 mcg/dL; a level that is considerably above the lower limit of the normal reference range (3.1 mcg/dL) as well as above the defined stimulated cut off level (18 mcg/dL). In addition, the 30 minute value was lower than the pre-test value, a clinically unusual result.

**Calcium metabolism:** There was no clinically relevant mean change in albumin-corrected serum calcium, 24-hour urinary calcium excretion or the urinary calcium:creatinine ratio. No subjects had albumin-corrected serum calcium values above the reference range at any visit. Most subjects recorded 24-hour urine calcium and calcium:creatinine ratio values within the reference range at baseline and did not record a shift at Days 28 and 56. Two subjects were identified with a possibly clinically relevant increase in 24-hour urinary calcium excretion. Calcipotriol and its metabolite (MC1080) were not detected in any of the PK samples from these subjects. Overall there were no changes of clinical concern regarding the effect on calcium metabolism.

**Pharmacokinetics:** None of the PK parameters could be calculated because only a minority of subjects had values above the lower detection limit. The main metabolite of calcipotriol, MC1080, was below the LLOQ (20 pg/mL) in all samples. Out of the 271 samples analysed for the metabolite of betamethasone dipropionate (betamethasone 17-propionate), concentrations above the LLOQ (30 pg/mL) were determined in 56 samples from 16 subjects at concentrations between 30.5 - 257 pg/mL. Betamethasone dipropionate was measurable in one sample each from five different subjects.

**Clinical efficacy:** The percentage of subjects with ‘controlled disease’ was 16.3% at Day 28 (Visit 3), 28.9% at Day 56 (Visit 5) and 27.9% at the end of treatment.

**SAFETY RESULTS:** There were no deaths reported. Thirteen (30.2%) subjects reported 17 AEs. One AE, myelocyte count, was considered serious and possibly related to the study drug. The most common AEs by preferred term were adrenal suppression (3 subjects), and hypertension (2 subjects). All other preferred terms were reported for one subject only. The majority of AEs were not considered treatment-related by the investigators. Adverse drug reactions were reported by six subjects (14.0%). The most common ADR was adrenal suppression reported for 3 (7.0%) subjects. Four subjects withdrew at Day 28 (Visit 3) due to AEs; three of these subjects were withdrawn for adrenal suppression as per protocol and one subject was withdrawn for hypertension deemed unrelated to treatment. There were no changes of clinical concern in any of the other routine laboratory parameters assessed or vital signs.
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LEO Pharma A/S

**Name of Finished Product:**
DAIVOBET/DOVOBET gel

**Name of Active Ingredient:**
Calcipotriol + Betamethasone dipropionate

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<th>Individual Trial Table</th>
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**CONCLUSION:** In subjects with very extensive psoriasis involving the scalp and non-scalp areas of the body (trunk and/or limbs), DAIVOBET/DOVOBET gel may have effects on the HPA axis but the incidence was low and did not increase over time even in this maximum use setting. Overall there were no changes of clinical concern regarding the effect on calcium metabolism and the clinical benefit and AE profile of DAIVOBET/DOVOBET gel was similar to that seen in other studies in psoriasis vulgaris.

**Date of the Report:** 23-NOV-2011