SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	(For National Authority Use only)
Name of Investigational Product/ Finished Product, if available: DAIVOBET/DOVOBET gel (LEO80185)	Volume:	
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Title of study/Protocol Code Number:

Long-term Treatment of Scalp Psoriasis with Calcipotriol plus Betamethasone Dipropionate Gel/MBL 0407 INT

Centre details:

Multicentre study conducted at 57 centres (Canada: 20; Germany: 6; Denmark: 2, France: 22; United Kingdom: 7)

Publication references:

To be decided.

Study period details:	Phase of development:
First patient included: 08-Feb-2005 Last patient attended last visit: 06-Jul-2006	III

Objectives/hypothesis, if applicable:

To study the safety of calcipotriol plus betamethasone dipropionate gel (henceforth referred to as DAIVOBET/DOVOBET gel) for long-term treatment of scalp psoriasis (up to 52 weeks).

Study methodology:

An international, multicentre, prospective, randomised, double blind, active-controlled, 2-arm, parallel group, 52-week safety study.

Patients were randomised, in a 1:1 ratio, to receive once daily treatment for up to 52 weeks with either 1) DAIVOBET/DOVOBET gel or 2) calcipotriol in the gel vehicle. Prior to randomisation (Visit 1), a washout period was to be completed if the patient was receiving, or had recently received, antipsoriatic treatments or other relevant medication, as defined in the exclusion criteria. Visits were scheduled every 4 weeks, between Weeks 0 and 52. A follow-up visit took place 14 days after the patient's last on-treatment visit if a treatment

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related adverse event (AE) (possible, probable or not assessable relationship to study medication) was ongoing.

Safety and efficacy assessments were made at each study visit. Safety parameters included AEs, adverse drug reactions (ADRs) and AEs of concern associated with long-term corticosteroid use on the scalp. Efficacy assessments included the Investigator's Global Assessment of disease severity and the patient's overall assessment of treatment response. Patients whose scalp psoriasis cleared at any time during the study remained in the study but stopped treatment for their scalp psoriasis, they could restart study treatment at a later date if their scalp psoriasis needed further treatment. Based on blinded data, an Adjudication Committee of three independent dermatologists evaluated all AEs reported throughout the study (AEAC) in order to identify AEs of concern associated with long-term corticosteroid use on the scalp.

Number of patients enrolled:

A total of 800 patients were planned (400 in each group). A total of 873 patients were enrolled and 869 were randomised: 429 to DAIVOBET/DOVOBET gel and 440 to calcipotriol in the gel vehicle. The safety analysis set comprised 419 patients who received DAIVOBET/DOVOBET gel and 431 who received calcipotriol in the gel vehicle.

Diagnosis and main criteria for patient selection:

Hospital out-patients or patients attending the private practice of a dermatologist or a general practitioner experienced in treating psoriasis vulgaris, aged 18 years or above, with a diagnosis of scalp psoriasis amenable to topical treatment with a maximum of 100 g of study medication per week. Extent of scalp psoriasis involving more than 10% of the total scalp area and a disease severity on the scalp graded as at least 'Moderate' according to the Investigator's Global Assessment of disease severity. Written informed consent given.

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

DAIVOBET/DOVOBET gel: calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) gel applied topically once daily to affected areas of the scalp as required by the patient. Lot numbers: 04 224 61 01 , 04 257 61 01, 04 258 61 01, 04 259 61 01, 04 219 61 01, 04 222 61 01

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

Calcipotriol 50 mcg/g in the gel vehicle. The reference product was applied topically once daily to affected areas of the scalp as required by the patient. Lot numbers: 04 264 61 01, 04 265 61 01, 04 271 61 01, 04 272 61 01, 04 273 61 01, 04 325 61 01

Duration of treatment:

Up to 52 weeks

Criteria for evaluation

Safety:

Primary response criteria: Incidence of ADRs of any type.

Incidence of AEs of concern associated with long-term corticosteroid use on the scalp.

Secondary response criteria: The incidence of AEs of any type.

Reasons for withdrawal from the study.

Efficacy:

Secondary response criteria: Percentage of visits in which patients had 'Satisfactorily controlled disease' ('Absence of disease', 'Very mild disease' or 'Mild disease') according to Investigator's Global Assessment of disease severity.

Incidence of patients with 'Satisfactorily controlled disease' at each visit.

Percentage of visits in which patients report having a 'Satisfactory' response to treatment

Incidence of patients reporting a 'Satisfactory' response to treatment at each visit.

Statistical methodology:

The proportion of patients who experienced ADRs and the proportion of patients who experienced AEs of concern associated with long-term topical corticosteroid use on the scalp were compared between treatment groups using chi-square tests, as was the proportions of patients reporting AEs of any type, lesional/perilesional AEs on the scalp, and AEs on the face. The main efficacy criterion (percentage of post-baseline 'Satisfactorily controlled disease' assessments according to the Investigator's Global Assessment of disease severity) was analysed using the Wilcoxon rank-sum non-parametric test.

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Summary - Conclusions

Safety results:

The percentage of patients reporting ADRs was statistically significantly lower in the DAIVOBET/DOVOBET gel group compared with the calcipotriol in the gel vehicle group.

Patients with:	Daivobet (n=419)	Calcipotriol (n=431)	Odds ratio[1] (95% CI)
at least one (≥1) ADR	72 (17.2%)	127 (29.5%)	0.50 (0.36-0.69) P<0.001
≥1 AE associated with long/term corticosteroid use	11 (2.6%)	13 (3.0%)	0.87 (0.38-1.96) p=0.73
≥1 AE	280 (66.8%)	310 (71.9%)	0.79 (0.59-1.05) P=0.11
≥1 lesional/perilesional AE on the scalp	50 (11.9%)	93 (21.6%)	0.49 (0.34-0.72) P<0.001
≥1 AE on the face	63 (15.0%)	79 (18.3%)	0.79 (0.55-1.13) P=0.20

[1] Chi squared test

DAIVOBET/DOVOBET gel was not associated with an increase in the percentage of patients reporting AEs of concern associated with long-term use of topical corticosteroids on the scalp. The events identified by the AEAC were similar in nature and frequency for the two treatment groups. The events reported by more than one patient in either group were: rosacea, folliculitis and dermatitis (verbatim term: perioral dermatitis) in the DAIVOBET/DOVOBET gel group (all reported by 0.7% of patients), and in the calcipotriol in the gel vehicle group: rosacea (1.2%), folliculitis (0.7%) and acne (0.5%). In the DAIVOBET/DOVOBET gel group there was one case of rash pustular and one case of acne. No cases of skin atrophy or striae were reported.

In general, the incidence for common ADRs (reported by ≥2.0% patients) was similar for the two treatment groups with the exception of pruritus and skin irritation, which were more frequently reported in the calcipotriol in the gel vehicle group. There were no new common ADRs in patients exposed for ≥12 months in the DAIVOBET/DOVOBET gel group.

Pain of the skin (2.1%) was a new common ADR in patients exposed for ≥12 months in the

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calcipotriol in the gel vehicle group, which was not observed at the 2.0% threshold for the full safety analysis set. There was no indication of any ADR increasing in frequency during 6-12 versus 0-6 months exposure. Overall the percentage of patients reporting AEs was lower in the DAIVOBET/DOVOBET gel group (66.8%) compared with the calcipotriol in the gel vehicle group (71.9%) but the difference did not reach statistical significance.
The percentage of patients reporting lesional/perilesional AEs on the scalp was lower in the DAIVOBET/DOVOBET gel group compared with the calcipotriol in the gel vehicle group. Pruritus (4.3%) was the only lesional/perilesional AE on the scalp reported at an incidence of ≥2.0% in the DAIVOBET/DOVOBET gel group. However, in the calcipotriol in the gel vehicle group, pruritus (10.0%), skin irritation (3.9%), burning sensation (2.6%) and erythema (2.1%) were reported at an incidence ≥2.0%.
Skin irritation was the most common AE reported on the face in the calcipotriol in the gel vehicle group occurring with higher incidence (3.5%) compared with the DAIVOBET/DOVOBET gel group (0.2%). Psoriasis was also a common AE on the face and occurred with similar incidence in both groups (3.3% in DAIVOBET/DOVOBET gel group and 3.2% in the calcipotriol in the gel vehicle group).

There were two deaths during the study. One patient in the DAIVOBET/DOVOBET gel group died due to complications after surgery for a benign neoplasm of the colon and one patient in the calcipotriol in the gel vehicle group died due to a cardiac arrest. Neither death was considered related to study treatment.
Nineteen patients (4.5%) had 34 serious adverse events (SAEs) in the DAIVOBET/DOVOBET gel group; these were all considered unrelated to study treatment. Twenty-two patients (5.1%) in the calcipotriol in the gel vehicle group had 35 SAEs; these were all considered unrelated to study treatment except one case of sinus tachycardia (possibly related).

The frequency of withdrawals was lower in patients receiving DAIVOBET/DOVOBET gel 82 (19.6%) versus calcipotriol in the gel vehicle 166 (38.5%). The frequency of withdrawals due to ‘unacceptable AEs’ was lower in the DAIVOBET/DOVOBET group compared with

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the calcipotriol in the gel vehicle group; 9 (2.1%) patients versus 44 (10.2%), respectively.

Efficacy results:

The median percentage of visits per patient during the study period (Visits 2-14) with an assessment of 'Satisfactorily controlled disease' based on the Investigator's Global Assessment of disease severity was significantly greater in the DAIVOBET/DOVOBET gel group (92.3%) compared with the calcipotriol in the gel vehicle group (80.0%) ($p<0.001$).
In the DAIVOBET/DOVOBET gel group, 45.5% patients had 'Satisfactory controlled disease' at each visit whereas in the calcipotriol in the gel vehicle group 31.8% patients had 'Satisfactory controlled disease' at every visit.

The median percentage of visits during the study period (Visits 2-14) with a 'Satisfactory' assessment according to the patient's overall assessment of treatment response was 100.0% in both the DAIVOBET/DOVOBET gel group and the calcipotriol in the gel vehicle group. However, in the DAIVOBET/DOVOBET gel group, more patients (76.2%) assessed the treatment response as 'Satisfactory' at each visit than in the calcipotriol in the gel vehicle group (50.2%).

Conclusion:

Treatment of scalp psoriasis with once daily DAIVOBET/DOVOBET gel used, as needed, for up to 52 weeks was well tolerated with a lower incidence of ADRs than calcipotriol in the gel vehicle used under the same regimen. There was no indication of DAIVOBET/DOVOBET gel causing AEs of concern associated with long-term corticosteroid use on the scalp.

Once daily DAIVOBET/DOVOBET gel used, as needed, for the long-term treatment of scalp psoriasis was shown to have superior efficacy versus once daily calcipotriol (in same gel vehicle) used, as needed, based on the percentage of visits at which assessments of ´Satisfactorily controlled disease' was achieved.

Report date:

20 February 2007