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:	
Name of Active Substance: Calcipotriol + Betamethasone dipropionate	Page:	

Title of study/Protocol Code Number:
DAIVOBET/DOVOBET Gel Compared to DAIVONEX/DOVONEX Scalp Solution in Patients with Scalp Psoriasis / MBL 0503 INT

Centre details:
Multicentre study conducted at 17 centres (Belgium: 2; Canada: 8; Denmark: 2; France: 3; Sweden: 2)

Publication references:
To be decided

Study period details:	Phase of development:
First patient included on 27-Sep-2005 Last patient attended last visit on 17-May-2006	III

Objectives/hypothesis, if applicable:
The primary objective was to compare the efficacy of 8 weeks, once daily treatment of calcipotriol plus betamethasone dipropionate gel (henceforth referred to as DAIVOBET/DOVOBET gel) with twice daily treatment of DAIVONEX/DOVONEX scalp solution. Secondary objectives were to investigate the occurrence of, and time to, relapse and occurrence of rebound over a period of at least 8 weeks after end of treatment in patients with 'Controlled disease', to compare the safety of DAIVOBET/DOVOBET gel versus DAIVONEX/DOVONEX scalp solution and to compare the quality of life with DAIVOBET/DOVOBET gel versus DAIVONEX/DOVONEX scalp solution.

Study methodology:
An international, multicentre, prospective, randomised, investigator-blind, 2-arm, parallel group, 8 week study followed by an observation phase of up to 8 weeks, in patients with scalp psoriasis. Patients were randomised in a 2:1 ratio to receive treatment for up to 8

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Name of Active Substance: Calcipotriol + Betamethasone dipropionate	Page:	

weeks with either DAIVOBET/DOVOBET gel, once daily or DAIVONEX/DOVONEX scalp solution, twice daily. Prior to randomisation (day 0) a washout period was completed if the patient had received anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria. Visits were performed on day 0 (baseline) and after 1, 2, 4, 6 and 8 weeks. Patients graded as 'Clear' (according to the investigator's global assessment of disease severity) at an on-treatment visit prior to week 8 stopped treatment, but had study drug available if re-initiation of treatment was necessary. The initial study period was followed by a treatment-free observation period of 8 weeks for patients who had 'Controlled disease' according to the investigator's global assessment of disease severity at week 8. Patients were followed to investigate the occurrence of, and time to, relapse and occurrence of rebound. Visits took place at weeks 12 and 16 but an extra visit was scheduled if a patient was experiencing a worsening of scalp psoriasis and felt the need to reinitiate treatment. Patients experiencing relapse in the observation period ended the trial at that visit. A follow-up visit took place 14 (+/- 2) days after the patient's last on-treatment visit if a treatment related adverse event (possible, probable or not assessable relationship to the study medication) was ongoing at the patient's last on-treatment visit. At all visits (baseline to week 16) the investigator's global assessment of disease severity, investigator's assessment of extent of scalp psoriasis and assessment of clinical signs (redness, thickness and scaliness) and the patient's global assessment of disease severity and assessment of itching were performed. Quality of life assessment using SF-36v2 (in all countries) and Skindex-16 (in selected countries) were performed at baseline, weeks 2, 4 and 8. An assessment of product acceptability was performed at week 4.

Number of patients enrolled:

A total of 300 patients were planned (DAIVOBET/DOVOBET gel 200, DAIVONEX/DOVONEX scalp solution 100). A total of 312 patients were enrolled and randomised: 207 patients to DAIVOBET/DOVOBET gel and 105 patients to DAIVONEX/DOVONEX scalp solution.

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Name of Active Substance: Calcipotriol + Betamethasone dipropionate	Page:	

Diagnosis and main criteria for patient selection:

Hospital out-patients or patients attending the private practice of a dermatologist, aged 18 years or above, with a diagnosis of scalp psoriasis amenable to topical treatment with a maximum of 100 g DAIVOBET/DOVOBET gel or 60 ml DAIVONEX/DOVONEX scalp solution per week and with clinical signs of, or earlier diagnosis of, psoriasis vulgaris on trunk and/or limbs. Extent of scalp psoriasis involving 10% or more of the total scalp area and a score of at least 2 in one of the clinical signs (redness, thickness and scaliness) and at least 1 in each of the other two clinical signs. Disease severity on the scalp graded as at least moderate according to the investigator's global assessment of disease severity. 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 once daily for topical treatment of scalp psoriasis to a maximum of 100 g per week. Lot number: 042226101

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

DAIVONEX/DOVONEX scalp solution: calcipotriol 50mcg/ml applied twice daily for topical treatment of scalp psoriasis to a maximum of 60 ml per week. Lot number: 0522161

Duration of treatment:

The treatment period was up to 8 weeks.

Criteria for evaluation

Efficacy :

Primary response criterion:

Patients with 'Controlled disease' ('Clear' or 'Minimal' disease) according to investigator's global assessment of disease severity at week 8.

Secondary response criteria:

Patients with 'Controlled disease' ('Clear' or 'Minimal' disease) according to investigator's global assessment of disease severity at weeks 2 and 4

Patients with 'Success' (Total Sign Score ≤ 1) at week 8

For each clinical sign (redness, thickness and scaliness), patients with 'Success' (clinical sign score = 0) at week 8

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Name of Active Substance: Calcipotriol + Betamethasone dipropionate	Page:	

Patients with 'Controlled disease' ('Clear' or 'Very mild' disease) according to patient's global assessment of disease severity at week 8

Patients with relapse during the study and time to relapse

Patients with rebound during the study

Quality of Life and Product Acceptability:

Change in quality of life from baseline to week 2, 4 and 8 using SF-36 (v2) and Skindex-16

Product acceptability questionnaire at week 4

Safety:

Any reported adverse events or adverse drug reactions. Reasons for withdrawal from the study.

Statistical methodology

The primary response criterion was analysed based on the full analysis set and per protocol analysis set. Cochran-Mantel-Haenszel test was used to compare the two treatment groups regarding the proportion of patients with 'Controlled disease' according to the investigator's global assessment of disease severity at week 2, 4 and 8, the proportion of patients with 'Success' at week 8 according to the Total Sign Score (Total Sign Score ≤1) and for each clinical sign (redness, thickness, scaliness; score = 0) and the proportion of patients with 'Controlled disease' according to the patient's global assessment of disease severity at week 8. Descriptive statistics by treatment group were given for the proportion of patients with relapse, time to relapse and the proportion of patients with rebound. Quality of life data within and between the two treatment groups was compared using paired and two-sample t-tests.

Safety analysis of adverse events was carried out based on the safety analysis set. The proportions of patients who experienced adverse events, lesional/perilesional adverse events on the scalp and adverse drug reactions were compared between treatment groups using chi-square tests.

Summary – Conclusions:

Efficacy results:

Primary response criterion:

DAIVOBET/DOVOBET gel was statistically significantly more effective than

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Name of Active Substance: Calcipotriol + Betamethasone dipropionate	Page:	

DAIVONEX/DOVONEX scalp solution for the primary efficacy criterion: the proportion of patients with 'Controlled disease' (defined as 'Clear' or 'Minimal' disease) according to the investigator's global assessment of disease severity at week 8 (LOCF).

	Daivobet gel (n=207)	**DAIVONEX scalp solution (n=105)**
Controlled	142 (68.6%)	33 (31.4%)
Non controlled	65 (31.4%)	72 (68.6%)
Odds ratio		5.4
95% CI		3.1 to 9.4
P-value[1]		<0.001

[1] Cochran Mantel-Haenszel test adjusting for the effect of centre for the hypothesis of odds ratio equal to 1

There were no significant treatment by centre interactions and the analysis of the per protocol analysis set confirmed the results for the full analysis set.

The results for the secondary response criteria in the treatment phase of the study were as follows:

	Daivobet gel (n=207)	**DAIVONEX scalp solution (n=105)**
Controlled disease (investigator's global assessment of disease severity)		
Week 2 (LOCF)	125 (60.4%)	11 (10.5%)*
Week 4 (LOCF)	114 (55.1%)	19 (18.1%)*
Controlled disease (patient's global assessment of disease severity)		
Week 8 (LOCF)[1]	170 (82.1%)	36 (34.3%)*
Success at Week 8 (LOCF)		
Total Sign Score[2]	80 (38.6%)	11 (10.5%)*
Redness[3]	67 (32.4%)	11 (10.5%)*
Thickness[3]	124 (59.9%)	29 (27.6%)*
Scaliness[3]	76 (36.7%)	10 (9.5%)*

*Comparison statistically significant at a level of 0.7% in favour of Daivobet® Gel.

1. 'Clear' or 'Very mild disease'
2. Success; score 0 or 1
3. Success; score 0

Among the patients who had 'Controlled disease' (according to the investigator's global assessment of disease severity) at the end of the 8-week treatment phase and who entered

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the observation phase the occurrence of relapse and rebound was as follows:

	Daivobet gel (n=135)	**DAIVONEX scalp solution (n=29)**
Relapse	73 (54.1%)	10 (34.5%)
Median time to relapse	35 days	58 days
Rebound	2 (1.5%)	0 (0.0%)

Quality of Life and Product Acceptability Results:

The changes from baseline in the SF-36 (v2) general health questionnaire within the DAIVOBET/DOVOBET gel group were statistically significant for improvement in the Physical Component Summary at week 8 (P=0.005) and at weeks 2, 4 and 8 for the Mental Component Summary (week 2; P=0.002, week 4; P=0.017 and week 8; P=0.004). The only statistically significant change from baseline within the DAIVONEX/DOVONEX scalp solution group was in the Mental Component Summary at week 8 (P=0.040). There were no statistically significant differences between DAIVOBET/DOVOBET gel and DAIVONEX/DOVONEX scalp solution in the Physical Component Summary, the Mental Component Summary or any of the individual scales that make up these summaries. For the skin disease specific questionnaire (Skindex-16) the changes from baseline within both treatment groups were statistically significant for total sign score at weeks 2, 4 and 8 ($P<0.001$ for all timepoints). The difference in the total score between the two treatment groups was statistically significant in favour of DAIVOBET/DOVOBET gel at all time-points ($P<0.001$ at weeks 2 and 4 and P=0.008 at week 8). For the symptoms and emotions components of the Skindex-16, there were statistically significant differences between the two treatment groups in favour of DAIVOBET/DOVOBET gel at all timepoints (weeks 2, 4 and 8) but only at week 4 for the functioning component. The percentage of patients who answered 'Very acceptable' was higher for DAIVOBET/DOVOBET gel than for DAIVONEX/DOVONEX scalp solution for all product acceptability questions.

Safety results:

In the treatment phase of the study the proportion of patients with at least one adverse event was significantly lower in the DAIVOBET/DOVOBET gel group than in the DAIVONEX/DOVONEX scalp solution group; 71 (34.5%) patients versus 59 (56.7%)

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patients respectively, P<0.001. The proportion of patients with at least one adverse drug reaction in the treatment phase was significantly lower in the DAIVOBET/DOVOBET gel group than in the DAIVONEX/DOVONEX scalp solution group: 7 (3.4%) patients versus 28 (26.9%) patients respectively, P<0.001. The proportion of patients with at least one lesional/perilesional adverse event on the scalp in the treatment phase was significantly lower in the DAIVOBET/DOVOBET gel group than in the DAIVONEX/DOVONEX scalp solution group: 7 (3.4%) patients versus 20 (19.2%) respectively, P<0.001. Burning sensation was the most frequently reported adverse drug reaction and lesional/perilesional adverse event on the scalp in the DAIVOBET/DOVOBET gel group and occurred with similar incidence (1.0%) in both treatment groups. Pruritus, skin irritation and application site burning were the most frequently reported adverse drug reactions and lesional/perilesional adverse events on the scalp in the DAIVONEX/DOVONEX scalp solution group all of which were reported at higher incidences than in the DAIVOBET/DOVOBET gel group. In addition, erythema on the face was among the most frequently reported adverse drug reactions in the DAIVONEX/DOVONEX scalp solution group. Withdrawals due to adverse events in the treatment phase were lower in the DAIVOBET/DOVOBET gel group (1.0%) than in the DAIVONEX/DOVONEX scalp solution group (8.7%). In the observation phase no patients withdrew due to adverse events and incidences of adverse events in the two treatment groups were not statistically significantly different. There were no treatment related deaths or serious adverse events.

Conclusion:

DAIVOBET/DOVOBET gel was statistically significantly more effective than DAIVONEX/DOVONEX scalp solution when treating scalp psoriasis. The incidence of adverse events and adverse drug reactions reported during treatment with DAIVOBET/DOVOBET gel was significantly lower than with DAIVONEX/DOVONEX scalp solution. In conclusion when compared with DAIVONEX/DOVONEX scalp solution the benefit/risk ratio was in favour of DAIVOBET/DOVOBET gel.

Report date:

4 January 2007