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:

Calcipotriol plus betamethasone dipropionate gel compared to betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone in psoriasis vulgaris/MBL 0202 INT

Centre details:

Multicentre study conducted at 19 centres (Canada: 6; Germany: 4; Ireland: 1; Sweden: 3; United Kingdom: 5)

Publication references :

To be decided

Study period details:	Phase of development:
First patient included: 01 December 2005. Last patient attended last visit: 08 May 2006.	Phase II

Objectives/hypothesis, if applicable:

To compare the efficacy and safety of once daily treatment for up to 8 weeks of calcipotriol plus betamethasone dipropionate gel (henceforth referred to as DAIVOBET/DOVOBET gel) with betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone in patients with psoriasis vulgaris on the trunk and/or limbs.

Study methodology:

An international, multi-centre, prospective, randomised, double-blind, 4-arm, parallel group, 8-week study in patients with psoriasis vulgaris on the trunk and/or limbs.
Patients were randomised in a 4:2:2:1 ratio to receive once daily treatment for up to 8 weeks with either 1) DAIVOBET/DOVOBET gel or 2) betamethasone dipropionate in the gel vehicle or 3) calcipotriol in the gel vehicle or 4) gel vehicle

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Visits were performed at baseline (Visit 1) and after 7 (Visit 2), 14 (Visit 3), 28 (Visit 4), 42 (Visit 5) and 56 (Visit 6) days. A follow-up visit took place 14 days after the patient's last on-treatment visit if a treatment related adverse event (possible, probable or not assessable relationship to study medication) was ongoing. Prior to randomisation (Visit 1) a washout period was to be completed if the patient received anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria.
Efficacy assessments including the investigator's and the patient's global assessment of disease severity and the investigator's assessment of extent and clinical signs (redness, thickness and scaliness) were performed at all visits (Visits 1 to 6). Safety assessments were performed at all postrandomisation visits (Visits 2 to 6).

Number of patients enrolled:

A total of 360 patients were planned (DAIVOBET/DOVOBET gel 160, betamethasone dipropionate in the gel vehicle 80, calcipotriol in the gel vehicle 80, and the gel vehicle 40). A total of 374 patients were enrolled and 364 were randomised; 162 patients to DAIVOBET/DOVOBET gel, 83 to betamethasone dipropionate in the gel vehicle, 79 to calcipotriol in the gel vehicle, and 40 to the gel vehicle.

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 psoriasis vulgaris on the trunk and/or limbs amenable to treatment with a maximum of 100 g of topical medication per week and a disease severity of at least mild 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 topically once daily on affected areas on the trunk and/or limbs. Lot number: 04 222 61 01.

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

Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle. Lot numbers: 04 260 61 01 and

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04 261 61 01.
Calcipotriol 50 mcg/g in the gel vehicle. Lot number: 04 325 61 01.
Gel vehicle. Lot number: 04 263 61 01.
All reference products were applied topically once daily on affected areas on the trunk and/or limbs.

Duration of treatment:

The treatment period lasted for up to 8 weeks.

Criteria for evaluation

Efficacy :

Primary response criteria

Patients with 'controlled disease' according to the investigator's global assessment of disease severity at weeks 4 and 8. 'Controlled disease' was defined as 'clear' or 'minimal disease' for patients with at least moderate disease at baseline or 'clear' for patients with mild disease at baseline.

Secondary response criteria

Patients with 'controlled disease' according to the investigator's global assessment of disease severity at week 1, 2, and 6.
The absolute change in Psoriasis Area and Severity Index (PASI) from baseline to week 1, 2, 4, 6, and 8.
The percentage change in PASI from baseline to week 1, 2, 4, 6 and 8.
Patients with 'controlled disease' according to the patient's global assessment of disease severity at week 1, 2, 4, 6, and 8.

Safety:

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

Statistical methodology :

The efficacy analyses for the primary response criteria were based on the full analysis set and per protocol analysis set. The proportion of patients with 'controlled disease' according to the investigator's global assessment of disease severity was compared between the

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treatment groups using the Cochran-Mantel-Haenszel test. Analyses were performed for the following secondary response criteria; percentage change in PASI at weeks 4 and 8 on the full analysis set and the per protocol set, and 'controlled disease' according to the patient's global assessment of disease severity at weeks 4 and 8 on the full analysis set. 'Controlled disease' according to the patient's global assessment of disease severity was analysed in a similar way as the primary response criteria. Analysis of variance (ANOVA) was used to compare the percentage change from baseline in PASI. Safety analysis was carried out based on the safety analysis set. The proportion of patients who experienced adverse events and the proportion of patients who experienced adverse drug reactions were compared between the treatment groups using the chi-squared test.

Summary – Conclusions

Efficacy results:

Primary Response Criterion: DAIVOBET/DOVOBET gel was statistically significantly more effective than betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle at week 8 but at week 4, the comparison with betamethasone dipropionate in the gel vehicle did not reach statistical significance.

	Daivobet (n=162)	**Betamethasone (n=83)**	**Calcipotriol (n=79)**	**Gel vehicle (n=40)**
Week 4 (LOCF)				
Controlled	26 (16.0%)	8 (9.6%)	3 (3.8%)	1 (2.5%)
Non Controlled	136 (84.0%)	75 (90.4%)	76 (96.2%)	39 (97.5%)
Odds ratio		2.02	5.98	10.83
95% CI		0.84 to 4.82	1.53 to 23.34	1.04 to 112.73
P-value[1]		0.11	0.006	0.027
Week 8 (LOCF)				
Controlled	44 (27.2%)	14 (16.9%)	9 (11.4%)	0 (0.0%)
Non Controlled	118 (72.8%)	69 (83.1%)	70 (88.6%)	40 (100.0%)
Odds ratio		2.40	2.89	-
95% CI		1.11 to 5.20	1.31 to 6.38	-
P-value[1]		0.027	0.006	<0.0001

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

There were no 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 statistical analyses of the secondary response criteria were as follows:

	Daivobet (n=162)	**Betamethasone (n=83)**	**Calcipotriol (n=79)**	**Gel vehicle (n=40)**
% change in PASI from baseline to Week 4 (LOCF)				
Mean change (%)	-48.1	-40.9	-32.7	-16.9
Difference vs Daivobet® gel		-7.85	-15.4	-30.8
95% CI		-15.2 to -0.5	-22.8 to -7.9	-40.4 to -21.2
P-value[1]		0.04	<0.001	<0.001
% change in PASI from baseline to Week 8 (LOCF)				
Mean change (%)	-55.3	-49.8	-41.2	-11.9
Difference vs Daivobet® gel		-6.16	-13.9	-43.1
95% CI		-14.2 to 1.9	-22.0 to -5.7	-53.6 to -32.6
P-value[1]		0.13	<0.001	<0.001
Controlled disease (patient's global assessment of disease severity)				
Week 4 (LOCF)	48 (29.6%)	23 (27.7%)	11 (13.9%)*	3 (7.5%)*
Week 8 (LOCF)	69 (42.6%)	35 (42.2%)	16 (20.3%)*	4 (10.0%)*

*comparison statistically significant at a level of 5% in favour of Daivobet® gel

Safety results:

The proportion of patients with at least one adverse event was not statistically significantly different in the DAIVOBET/DOVOBET gel group (42.5%) compared with the betamethasone dipropionate in the gel vehicle group (48.2%; P=0.60), the calcipotriol in the gel vehicle group (35.4%; P=0.49) and the gel vehicle group (55.0%; P=0.39). The proportion of patients with at least one adverse drug reaction was not statistically significantly different in the DAIVOBET/DOVOBET gel group (8.1%) compared with the betamethasone dipropionate in the gel vehicle group (7.2%; P=0.82), the calcipotriol in the gel vehicle group (11.4%; P=0.46) and the gel vehicle group (20.0%; P=0.06). Le-

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sional/perilesional adverse events on the body (trunk/limbs) occurred in 12 patients (7.5%) in the DAIVOBET/DOVOBET gel group, 7 (8.4%) in the betamethasone dipropionate in the gel vehicle group, 8 (10.1%) in the calcipotriol in the gel vehicle group versus 10 (25.0%) in the gel vehicle group. The most frequently reported lesional/perilesional adverse event was dry skin in the DAIVOBET/DOVOBET gel group, pruritus and psoriasis in the betamethasone dipropionate in the gel vehicle group and pruritus in the calcipotriol in the gel vehicle and the gel vehicle groups. [redacted] patient [redacted] in the DAIVOBET/DOVOBET gel group reported lesional/perilesional pruritus. Adverse events were recorded as the reason for withdrawal for [redacted] patients in the DAIVOBET/DOVOBET gel group, [redacted] patients in the calcipotriol in the gel vehicle group and [redacted] patients in the gel vehicle group. No patients in the betamethasone dipropionate in the gel vehicle group withdrew due to adverse events. The [redacted] patients in the DAIVOBET/DOVOBET gel group withdrew due to application site burning and pain of skin. However, all other adverse drug reactions reported for DAIVOBET/DOVOBET gel were of mild or moderate intensity. [redacted] patients had 3 serious adverse events all unrelated to study treatment (one each in the DAIVOBET/DOVOBET gel, betamethasone dipropionate in the gel vehicle and calcipotriol in the gel vehicle groups) and there were no deaths.

Conclusion:

DAIVOBET/DOVOBET gel showed increasing efficacy at each post randomisation visit and the percentage of patients with controlled disease was higher than for betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle alone at each visit. This effect was statistically significant compared with betamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel vehicle at week 8, and compared with calcipotriol in the gel vehicle and the gel vehicle at week 4. There were no statistically significant differences between DAIVOBET/DOVOBET gel and the other treatments with regard to adverse events and adverse drug reactions.

Report date:

16-OCT-2008