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 and Calcipotriol in the Gel Vehicle in Scalp Psoriasis / MBL 0406 INT

International Co-ordinating Investigator:

[redacted], MD, Afdeling Dermatologie, Universitair Medisch, [redacted], The Netherlands

Centre details [number by country]:

Multicentre study conducted at 98 centres (Belgium: 11; Canada: 6; Finland: 7; France: 7; Germany: 14; Ireland: 4; Netherlands: 8; United Kingdom: 41).

Publication references :

To be decided.

Study period details: date of first enrolment, date of last patient completed:	Phase of development:
First patient included 08 December 2004 Last patient attended last visit 12 September 2005	Phase III

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 and calcipotriol in the gel vehicle in patients with scalp psoriasis

Study: methodology, design, assessments, stratification:

An international, multicentre, prospective, randomised, double-blind, 3-arm, parallel group, 8-week study in patients with scalp psoriasis.

Patients were randomised in a 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.

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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 treatment) was ongoing. Prior to randomisation (Visit 1) a washout period was to be completed if the patient was receiving anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria.

Prior to Amendments 1 & 2 patients graded to have 'Absence of disease' according to the Investigator's Global Assessment of Disease Severity at any of Visits 2-5 exited the study but post Amendments 1 & 2 they remained in the study until Visit 6 and restarted treatment if required.

Efficacy assessments including the Investigator's Global Assessment of Disease Severity, extent of scalp psoriasis and assessment of the clinical signs (redness, thickness and scaliness) were performed at all visits (1 to 6). At Visits 2 to 6 the patients made an overall assessment of their treatment response compared to baseline. Safety assessments were performed at all post-baseline visits (Visits 2 to 6 and follow-up). Blood samples for albumin corrected calcium measurements were taken at baseline and at weeks 1 and 4 (Visits 2 and 4).

Number of patients enrolled:

A total of 1350 patients were planned (DAIVOBET/DOVOBET gel 540, betamethasone dipropionate in the gel vehicle 540, calcipotriol in the gel vehicle 270). A total of 1418 patients were enrolled and 1417 were randomised: 568 to DAIVOBET/DOVOBET gel 563 to betamethasone dipropionate in the gel vehicle and 286 to 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 and with clinical signs of or an earlier diagnosis of psoriasis vulgaris on trunk and/or limbs. Extent of scalp psoriasis involving more than 10% of the scalp area and a score of at least 2 in one of the clinical signs (redness, thickness and scaliness) and at

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least 1 in each of the other two clinical signs. Disease severity on the scalp graded as at least 'Mild' according to the Investigator's Global Assessment of Disease Severity (prior to Amendments 1 & 2) and at least 'Moderate' (post Amendments 1 & 2). 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 to affected areas on the scalp once daily to a maximum of 100 g per week. Lot numbers : [redacted] and [redacted]

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

Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle. Lot numbers: [redacted] and [redacted]

Calcipotriol 50 mcg/g in the gel vehicle. Lot numbers: [redacted] and [redacted]

Both reference products were applied topically to affected areas on the scalp once daily.

Duration of treatment:

Up to 8 weeks.

Criteria for evaluation

Efficacy :

Primary Response Criterion: (post Amendments 1 & 2)

Patients with 'Controlled disease' ('Absence of disease' or 'Very Mild Disease') according to Investigator's Global Assessment of Disease Severity at week 8

Secondary Response Criteria (post Amendments 1 & 2):

Patients with 'Controlled disease' ('Absence of disease' or 'Very mild disease') according to Investigator's Global Assessment of Disease Severity at weeks 2 and 4

Total Sign Score at week 8

Score for scaliness, redness and thickness at week 8

Patients with 'Treatment success' ('Almost clear' or 'Cleared') according to the Patient's overall assessment of treatment response at week 8.

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Safety:

Any reported adverse events, or adverse drug reactions. Reasons for withdrawal from the study. The absolute change in laboratory values (albumin corrected calcium) from baseline (Visit 1) to weeks 1 and 4 (Visits 2 and 4).

Statistical methodology

The primary response criterion was analysed based on the full analysis set and the per protocol analysis set. The proportion of patients who achieved 'Controlled disease' at week 8 last observation carried forward (LOCF) was compared between the treatment groups using the Cochran-Mantel-Haenszel test adjusting for the effect of centre. For each of the comparisons, the odds ratio (OR) (odds of 'Controlled disease' for DAIVOBET/DOVOBET gel relative to that for each of the other treatments), its 95% confidence interval and P-value was calculated. The Breslow-Day test for homogeneity of the odds ratio across centres was calculated for each treatment comparison. The secondary response criteria were all dichotomised into success/failure and analysed in a similar way based on the full analysis set using a 0.7% level of significance to account for multiplicity.

Safety analysis of adverse events was carried out based on the safety analysis set. The number of patients experiencing each type of adverse event (according to the coding system) was tabulated by treatment group regardless of the number of times each adverse event was reported by each patient. The proportion of patients with adverse events was compared between treatment groups by chi-square test.

Summary – Conclusions

Efficacy results:

Primary response criterion:

DAIVOBET/DOVOBET gel was statistically significantly more effective than betamethasone dipropionate in the gel vehicle and calcipotriol in the gel vehicle for the primary efficacy criterion: the proportion of patients with 'Controlled disease' (defined as 'Absence of disease' or 'Very mild disease') at week 8 (LOCF).

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	Daivobet Gel (n=567)	Betamethasone (n=562)	Calcipotriol (n=286)
Controlled	388 (68.4%)	343 (61.0%)	124 (43.4%)
Non controlled	179 (31.6%)	219 (39.0%)	162 (56.6%)
Odds ratio		1.41	3.13
95% CI		1.09-1.81	2.29-4.28
P-value1		0.0079	<0.0001

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

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

The results for the secondary response criteria were as follows:

	Daivobet Gel (n=567)	Betamethasone (n=562)	Calcipotriol (n=286)
Controlled disease			
Week 2 (LOCF)	278 (49.0%)	216 (38.4%)*	45 (15.7%)*
Week 4 (LOCF)	311 (54.9%)	287 (51.1%)	74 (25.9%)*
Success at Week 8 (LOCF)			
Total Sign Score[1]	314 (55.4%)	252 (44.8%)*	86 (30.1%)*
Redness[2]	238 (42.0%)	190 (33.8%)*	67 (23.4%)*
Thickness[2]	410 (72.3%)	338 (60.1%)*	145 (50.7%)*
Scaliness[2]	294 (51.9%)	249 (44.3%)	74 (25.9%)*
Patient's overall assessment[3]	392 (69.6%)	333 (59.9%)*	126 (44.7%)*

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

1. Success;score 0 or 1
2. Success;score 0
3. Success; 'Almost clear' or 'Cleared'

Safety results:

The safety results for DAIVOBET/DOVOBET gel and betamethasone dipropionate in the gel vehicle were similar and favourable compared with calcipotriol in the gel vehicle. The proportion of patients with at least one adverse event was similar in the DAIVOBET/DOVOBET gel and betamethasone dipropionate in the gel vehicle groups: 218

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(38.7%) and 228 (41.0%), P=0.43 but statistically significantly higher in the calcipotriol in the gel vehicle group, 130 (46.1%) than in the DAIVOBET/DOVOBET gel group P=0.04. Lesional/perilesional adverse events on the scalp occurred in 35 patients (6.2%) in the DAIVOBET/DOVOBET gel group and 32 (5.8%) in the betamethasone dipropionate in the gel vehicle group, versus 36 (12.8%) in the calcipotriol in the gel vehicle group. Pruritus was the most frequently reported lesional/perilesional adverse event on the scalp (DAIVOBET/DOVOBET gel 2.1%, betamethasone dipropionate in the gel vehicle 1.3% and calcipotriol in the gel vehicle 8.9%). Pruritus was the only lesional/perilesional adverse event reported by > 1% of patients in the DAIVOBET/DOVOBET gel and betamethasone dipropionate in the gel vehicle groups. In the calcipotriol group, skin irritation and burning sensation were also reported by > 1% of patients.

There was one death (due to pneumonia) in the calcipotriol in the gel vehicle group, which was considered unrelated to study treatment. Eleven patients had 12 serious adverse events (4 in each group) which were all unrelated to study treatment. There were no changes of clinical concern in serum corrected calcium.

Conclusion:

DAIVOBET/DOVOBET gel was statistically significantly more effective when treating scalp psoriasis than betamethasone dipropionate and calcipotriol in the same gel formulation. The incidence of lesional/perilesional adverse events with DAIVOBET/DOVOBET gel was low, similar to betamethasone dipropionate in the gel vehicle and significantly lower than calcipotriol in the gel vehicle. In conclusion DAIVOBET/DOVOBET gel was found to be effective and safe in the treatment of scalp psoriasis and the benefit/risk ratio was favourable.

Report date:

19 May 2006