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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 dipropion- ate	Page:	
Title of study/Protocol Code Number: Calcipotriol plus Betamethasone Dipropionate Gel Compared to Betamethasone Dipropion- ate in the Gel Vehicle, Calcipotriol in the Gel Vehicle and the Gel Vehicle alone in Scalp Psoriasis / MBL 0405 INT.		
International Co-ordinating Investigator: Dr. [REDACTED], Medical department, Roskilde Amtssygehus, [REDACTED] [REDACTED], Denmark.		
Centre details Multicentre study conducted at 101 centres (Canada 15; Denmark 4; France 25; Norway 10; Portugal 2; Spain 10; Sweden 11; United Kingdom 24).		
Publication references To be determined.		
Study period details First patient included on 17 November 2004 Last patient attended last visit on 08 September 2005		Phase of development: Phase III
Objectives/hypothesis, if applicable: Main objective: 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 scalp psoriasis.		
Study methodology, [design, assessments, stratification]: An international, multicentre, prospective, randomised, double-blind, 4-arm, parallel group, 8-week study in patients with scalp psoriasis. Patients were randomised in a 4:4:2:1 ratio to receive once daily treatment for up to 8 weeks		



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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.

Visits were performed on day 0 (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 (possible, probable or not assessable relationship to treatment) adverse event 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 Protocol Amendment No. 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 Amendment No. 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, assessment of the clinical signs (redness, thickness and scaliness) were performed at all visits (1 to 6) and the patient's overall assessment of response to treatment at visits 2 to 6. Safety assessments were performed at all post-baseline visits. Blood samples for analysis of serum calcium and albumin were taken at baseline and at Weeks 1 and 4 (Visits 2 and 4).

Number of patients enrolled

A total of 1485 patients were planned (DAIVOBET/DOVOBET gel 540, betamethasone dipropionate in the gel vehicle 540, calcipotriol in the gel vehicle 270 and gel vehicle 135). A total of 1506 patients were enrolled and 1505 were randomised; 541 patients to DAIVOBET/DOVOBET, 556 to betamethasone dipropionate in the gel vehicle, 272 to calcipotriol in the gel vehicle and 136 to 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



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Name of Active Substance: Calcipotriol + Betamethasone dipropion- ate	Page:	

study medication per week and with clinical signs of or an earlier diagnosis of psoriasis vulgaris on the 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 (erythema, thickness and scaliness) and at 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 Amendment 2 and at least 'Moderate' post Amendment 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 no. (expiry date): [REDACTED] (08 2006), [REDACTED] (08 2006), [REDACTED] (08 2006), [REDACTED] (08 2006), [REDACTED] (08 2006)

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

- Betamethasone 0.5 mg/g (as dipropionate) in the gel vehicle. Lot no. (expiry date): [REDACTED] (08 2006), [REDACTED] (08 2006)
- Calcipotriol 50 mcg/g in the gel vehicle. Lot no. (expiry date): [REDACTED] (09 2006), [REDACTED] (09 2006), [REDACTED] (09 2006), [REDACTED] (10 2006)
- Gel vehicle. Lot no. [REDACTED] (expiry 09 2006)

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

Duration of treatment:
The treatment period was up to 8 weeks.

Criteria for evaluation

Efficacy:

Primary response criterion: (post Amendment No. 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 Amendment No. 2):
Patients with 'Controlled disease' according to Investigator's Global Assessment of disease



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Name of Active Substance: Calcipotriol + Betamethasone dipropion- ate	Page:	

severity at Week 2 and 4.
Total Sign Score at Week 8
Score for redness, thickness and scaliness at Week 8
Patients with 'Treatment success' ('Almost clear' or 'Cleared') according to patient's overall assessment of response to treatment from visit 1 to Week 8.

Safety:
Any reported adverse events or adverse drug reactions. Reasons for withdrawal from the study. The absolute change in laboratory values from baseline (Visit 1) to Weeks 1 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 (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 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 be-
tamethasone dipropionate in the gel vehicle, calcipotriol in the gel vehicle and the gel



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Name of Active Substance: Calcipotriol + Betamethasone dipropion- ate	Page:	

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 for the full analysis set.

	Daivobet (n=541)	Betamethasone (n=556)	Calcipotriol (n=272)	Vehicle (n=136)
Controlled	385 (71.2%)	356 (64.0%)	100 (36.8%)	31 (22.8%)
Non Controlled	156 (28.8%)	200 (36.0%)	172 (63.2%)	105 (77.2%)
Odds ratio		1.41	4.13	8.65
95% CI		1.08-1.83	3.00-5.70	5.52-13.56
P-value ¹		0.011	<0.0001	<0.0001

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

There was a significant treatment by centre interaction for the comparison with calcipotriol (P=0.0084, Breslow-Day test). 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 (n=541)	Betamethasone (n=556)	Calcipotriol (n=272)	Vehicle (n=136)
Controlled disease				
Week 2 (LOCF)	311 (57.5%)	262 (47.1%)*	51 (18.8%)*	16 (11.8%)*
Week 4 (LOCF)	362 (66.9%)	304 (54.7%)*	64 (23.5%)*	20 (14.7%)*
Success at Week 8 (LOCF)				
TSS ¹	286 (52.9%)	266 (47.8%)	68 (25.0%)*	17 (12.5%)*
Redness ²	220 (40.7%)	209 (37.6%)	60 (22.1%)*	14 (10.3%)*
Thickness ²	364 (67.3%)	356 (64.0%)	110 (40.0%)*	36 (26.5%)*
Scaliness ²	289 (53.4%)	260 (46.8%)	65 (23.9%)*	16 (11.8%)*
Patients overall assessment ³	363 (68.6%)	344 (62.5%)	102 (38.3%)*	28 (20.7%)*

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

¹ Success; score of 0 (none) or 1 (slight)

² Success; score of 0 (none) or 1 (slight)

³ Success; 'Almost clear' or 'Cleared'

Safety results:

The safety results for DAIVOBET/DOVOBET gel and betamethasone dipropionate in the



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Name of Active Substance: Calcipotriol + Betamethasone dipropion- ate	Page:	

gel vehicle were similar and favourable compared with calcipotriol in the gel vehicle and 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: 183 (34.5%) and 191 (34.9%), $P=0.91$. The proportion of patients with adverse events in the calcipotriol in the gel vehicle group, 123 (46.2%), was statistically significantly higher than in the DAIVOBET/DOVOBET gel group, $P=0.0014$, and although the proportion of patients with adverse events in the gel vehicle group, 54 (40%) was higher than in the DAIVOBET/DOVOBET gel group, the difference was not statistically significant, $P=0.24$. Lesional/perilesional adverse events were reported for 25 (4.7%) patients in the DAIVOBET/DOVOBET gel group and 29 (5.3%) in the betamethasone dipropionate in the gel vehicle group, versus 35 (13.2%) in the calcipotriol in the gel vehicle group and 18 (13.3%) in the gel vehicle group. Pruritus was the most frequently reported le-
sional/perilesional adverse event, experienced by 15 (2.8%) in the DAIVOBET/DOVOBET gel group and 10 (1.8 %) in the betamethasone dipropionate in the gel vehicle group, compared with 16 (6.0%) in the calcipotriol in the gel vehicle group and 9 (6.7%) in the gel vehicle group. There were no other lesional/perilesional adverse events reported by >1% of patients in either the DAIVOBET/DOVOBET gel or betamethasone dipropionate in the gel vehicle groups. Pruritus, burning sensation, skin burning sensation, psoriasis, and skin irritation were reported by >1% of patients in the calcipotriol in the gel vehicle group; and psoriasis, pain, alopecia and skin irritation were reported by >1% in the gel vehicle group. There were no deaths during the study. Nine patients had 12 serious adverse events, which were all unrelated to study treatment (two patients had four serious adverse events in the DAIVOBET/DOVOBET gel group, two patients had two serious adverse events in the betamethasone dipropionate in the gel vehicle group, four patients had five serious adverse events in the calcipotriol in the gel vehicle group and one patient had one serious adverse event in the gel vehicle group). There were no changes of clinical concern in serum cor-
rected calcium.



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<p>Conclusion:</p> <p>DAIVOBET/DOVOBET gel was statistically significantly more effective when treating scalp psoriasis than betamethasone dipropionate, calcipotriol or vehicle 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 and the gel vehicle. In conclusion DAIVOBET/DOVOBET gel was found to be safe and effective in the treatment of scalp psoriasis and the benefit/risk ratio is favourable.</p>		
<p>Report date:</p> <p>22 May 2006</p>		

