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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 ointment DAIVONEX/DOVONEX cream	Volume:	
Name of Active Substance: Calcipotriol, betamethasone dipropionate	Page:	
Title of study/Protocol Code Number: Different treatment regimens of calcipotriol cream and combination (calcipotriol/ betamethasone dipropionate) ointment in psoriasis vulgaris/ MCB 0402 INT		
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Centre details 12 centres in Belgium, 12 in Canada, 6 in Germany, 7 in Spain, 15 in France, 3 in The Netherlands and 22 in the UK to give a total of 77.		
Publication references White S, Vender R, Thaci D, et al. Use of calcipotriene cream (Dovonex <sup>®</sup> cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex <sup>®</sup> ). Am J Clin Dermatol 2006; 7(3):177-84.		
Study period details First patient enrolled 21 Apr 2005 Last patient completed follow-up 13 Dec 2005	Phase of development: Phase IV.	
Objectives/hypothesis, if applicable: Primary objective: To compare the efficacy of 4 weeks of combination ointment followed by 8 weeks of calcipotriol cream (calcipotriol group) with 4 weeks of combination ointment followed by 8 weeks of calcipotriol cream (vehicle group) in the treatment of patients with psoriasis vulgaris. Secondary objective: To compare the efficacy of 4 weeks of combination ointment followed by 8 weeks of calcipotriol cream on weekdays (Monday to Friday)/combination ointment on weekends (Saturday and Sunday) (alternating group) with the vehicle group.		
Study methodology, Patients were randomised in a 1:1:1 ratio to receive 4 weeks of combination ointment followed by 8 weeks of either:		
<ul style="list-style-type: none"> <li>• calcipotriol cream</li> </ul>		

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<ul style="list-style-type: none"> <li>• calcipotriol cream on weekdays (Monday-Friday) and combination ointment on weekends (Saturday and Sunday), or</li> <li>• vehicle of calcipotriol cream.</li> </ul> <p>All medications in both phases were applied once daily to psoriasis of the trunk and/or limbs. After the first 4 weeks, medication was used when required. The study was partially double-blind, as it was possible to distinguish the alternating group from the other two groups by physical examination of the medication. Patients were seen at weeks 0, 2, 4, 6, 8 and 12. Investigator assessments were: Psoriasis Area and Severity Index (PASI), global assessment of disease severity on a 6-point scale (absent to very severe disease), and adverse events. Patient assessments were: global assessment of treatment response on a 7-point scale (worse than baseline to cleared).</p>		
Number of patients enrolled A total of 1138 patients were enrolled, and 1136 were randomised: 383 to the calcipotriol group, 377 to the alternating group, and 376 to the vehicle group.		
Diagnosis and main criteria for patient selection: Inclusion criteria: patients aged $\geq 18$ years with psoriasis vulgaris affecting at least 10% of arms and/or 10% of legs and/or 10% of the trunk and of at least a moderate severity. Exclusion criteria: patients with any contraindications to the study medications, use of concurrent medication which may affect psoriasis or with concurrent skin diseases that may confound the evaluation of psoriasis.		
Investigational product, dose, method of administration, lot numbers: DAIVOBET/DOVOBET ointment (combination ointment), containing calcipotriol 50 $\mu$ g/g plus betamethasone 0.5mg/g (as dipropionate), applied topically once daily for 4-12 weeks, depending on treatment group. Lot numbers: 051116301, 043386101. DAIVONEX/DOVONEX cream (calcipotriol cream), containing calcipotriol 50 $\mu$ g/g, applied topically once daily for 8 weeks. Lot numbers: 043386201, 051116201.		
Reference product, dose, method of administration, lot numbers: Vehicle of calcipotriol cream, applied topically once daily for 8 weeks. Lot numbers:		

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043396101, 043406201, 051126201, 043396201.		
Duration of treatment: Combination ointment: 4-12 weeks, depending on randomisation. Calcipotriol cream: 8 weeks. Vehicle of calcipotriol cream: 8 weeks		
Criteria for evaluation Efficacy : The primary response criterion is the percentage change in PASI from baseline (visit 1) to end of trial. The secondary response criteria are: The distribution of the investigators' global assessment of disease severity at the end of trial; the distribution of the patients' global assessment of treatment response at the end of trial; the percentage of patients who experience PASI-defined rebound and relapse during the study; and the absolute change in PASI during the last 8 weeks of the study. Safety: The number and percentage of patients with adverse events, adverse drug reactions, and serious adverse events.		
Statistical methodology For the primary response criterion, the mean percentage change in PASI from baseline to end of trial was compared between the calcipotriol and vehicle groups using an analysis of covariance model, including treatment, pooled centre and baseline PASI terms. The mean change in PASI from baseline to end of trial was compared between the alternating and vehicle groups as described above. For the distribution of the investigator's global assessment of disease severity and patient's global assessment of treatment response at end of trial, the Cochran-Mantel-Haenszel test was used for the two treatment comparisons: calcipotriol versus vehicle groups and alternating versus vehicle groups. The remainder of the secondary efficacy response criteria were tabulated by treatment group. The proportion of patients with adverse events and adverse drug reactions was compared between calcipotriol and vehicle groups, and between alternating and vehicle groups, using a chi squared test.		

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<p>Summary – Conclusions</p> <p>Of the 1136 randomised patients (383 in the calcipotriol group, 377 in the alternating group and 376 in the vehicle group), all 1136 were in the full analysis set. There were 1122 patients (379, 370 and 373, respectively) in the safety analysis set. The mean age of all patients was 50.7 years, 60.7% were male, 96.9% were Caucasian, the mean PASI at baseline was 8.9 and 76.0% of patients had moderate disease by the investigator’s global assessment of disease severity. In the calcipotriol group, 12.5% of patients withdrew, compared to 9.5% in the alternating group and 21.0% in the vehicle group.</p> <p>Efficacy results:</p> <p>The mean percentage change in PASI from baseline to end of trial was -44.5% for the calcipotriol group, -58.4% for the alternating group and -33.1% for the vehicle group. The mean difference between the calcipotriol and vehicle groups (primary treatment comparison) was -11.7% (95% CI: -17.9 to -5.5), which was statistically significant (P&lt;0.001). The mean difference between the alternating and vehicle groups was -24.7% (95% CI: -30.9 to -18.5), which was also statistically significant (P&lt;0.001). For the investigator’s global assessment of disease severity at the end of the trial, the differences between the calcipotriol and vehicle groups, and between the alternating and vehicle groups, were statistically significant (P&lt;0.001), showing superior efficacy in the non-vehicle groups. The results were similar for the patient’s global assessment of treatment response. The incidence of PASI defined rebound during the total study period was 4.8% of patients in the calcipotriol group, 2.4% in the alternating group and 10.2% in the vehicle group. The incidence of PASI defined relapse during the total study period was 37.3% of patients in the calcipotriol group, 18.6% in the alternating group and 46.6 % in the vehicle group. The mean absolute change in PASI during the last 8 weeks of the trial was 1.6 for the calcipotriol group, 0.5 for the alternating group and 3.2 for the vehicle group.</p> <p>Safety results:</p> <p>There were 40.4% of patients who experienced an adverse event in the calcipotriol group, 36.8% in the alternating group and 36.7% in the vehicle group. The difference between the calcipotriol and vehicle groups (odds ratio [OR] 1.17; 95% CI: 0.86 to 1.56; P = 0.31) and between the alternating and vehicle groups (OR 1.00; 95% CI: 0.74 to 1.35; P = 0.99) was</p>		

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<p>not statistically significant. There were [REDACTED] patients with serious adverse events in the calcipotriol group, seven in the alternating group and [REDACTED] in the vehicle group, all of which were considered unrelated to study treatment. There were 11.3% of patients in the calcipotriol group who experienced an adverse drug reaction, 7.6% in the alternating group and 8.6% in the vehicle group. The difference between the calcipotriol and vehicle groups (OR 1.36; 95% CI: 0.84 to 2.21; P = 0.21) and between the alternating and vehicle groups (OR 0.87; 95% CI: 0.51 to 1.48; P = 0.61) was not statistically significant. The most common ADRs were erythema, pruritus, psoriasis, rash scaly and skin irritation.</p> <p>Conclusion:                  Four weeks of treatment with combination (calcipotriol and betamethasone dipropionate) ointment followed by 8 weeks of maintenance treatment with calcipotriol cream is effective and safe in the treatment of patients with psoriasis vulgaris. As an alternative maintenance regimen, treatment with calcipotriol cream on weekdays and combination ointment on weekends is also effective and safe.</p>		
Report date: 05-JUN-2007		