

## SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regu- latory Dossier for authorities	(For National Authority Use only)
Name of Investigational Product/Finished Product, if available: Daivobet® ointment, Diprosalic® ointment, Betnovat® ointment, Dermovat® ointment, Elocon® ointment, Daivobet® ointment vehicle	Volume:	
Name of Active Substance: Calcipotriol plus betamethasone dipropionate, betamethasone dipropionate plus salicylic acid, betamethasone valerat, clobetasol-17-propionate, mometasonefuroate, Daivobet® ointment vehicle.	Page:	
Title of study: A plaque test comparing the anti-psoriatic effect of marketed products for topical use for psoriasis vulgaris / PLQ-002		
Trial sites: Single centre in France		
Publication (reference): Not applicable		
Studied period: Date of first enrolment: 27-JAN-2009 Date of last subject completed: 02-MAR-2009		Phase of development:
Objectives: To compare the anti-psoriatic effect of Daivobet® ointment, Diprosalic® ointment, Betnovat® ointment, Dermovat® ointment, and Elocon® ointment and the Daivobet® ointment vehicle using a plaque test method.		
Methodology: A single centre, investigator blinded within-subject randomised, active- and vehicle- controlled, repeated dose, translational phase 2 study. The study consisted of a Screening Visit, a wash-out period, a treatment period of 21 days, and if applicable, a follow-up visit. Within 21 days before treatment a screening for study eligibility of the subjects took place. Prior to Day 1 (Visit 2) a washout period (up to 21 days) was completed if the subject was treated or recently was treated with anti-psoriatic medication or other relevant treatments. Treatment products were given once daily 6 days a week for three (3) weeks. The subjects received study medication on six (6) test sites of 2-cm diameter selected on predetermined		

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lesions. Twice a week during the treatment phase clinical assessments were performed. At day 1 (baseline), 8, 15 and 22 (end of treatment period) ultrasound measurements of skin thickness were performed. During the treatment phase local and systemic adverse events were reported on an ongoing basis. If an adverse event (serious or non-serious), classified as possible or probably related to the study medication or not assessable in relation to the trial medication, was ongoing at the subject's last on-treatment visit, a follow-up visit took place 14 (±2) days after that visit.

Number of subjects enrolled:  
24 subjects

Diagnosis and main criteria for eligibility

**Main criteria for inclusion:**

1. Subjects having understood and signed an informed consent form
2. Either sex
3. Age 18 years or above
4. All skin types
5. Subjects with a diagnosis of psoriasis vulgaris with lesions located on arms, legs or trunk. The lesions must have a total size suitable for application of 6 different products. The subjects should be asked if their lesions have been stable for at least 1 month prior to inclusion
6. Subjects with, in the opinion of the investigator, stable psoriasis assessed by Total Plaque Score at screening visit and again at visit 2
7. Subjects with psoriasis lesions assessed by a Total Plaque Score (sum of scores of erythema, scaling and infiltration) of 4 to 9 inclusive but each individual item  $\geq 1$

**Main criteria for exclusion:**

1. Females who are pregnant, of child-bearing potential and who wish to become pregnant during the study, or who are breast feeding

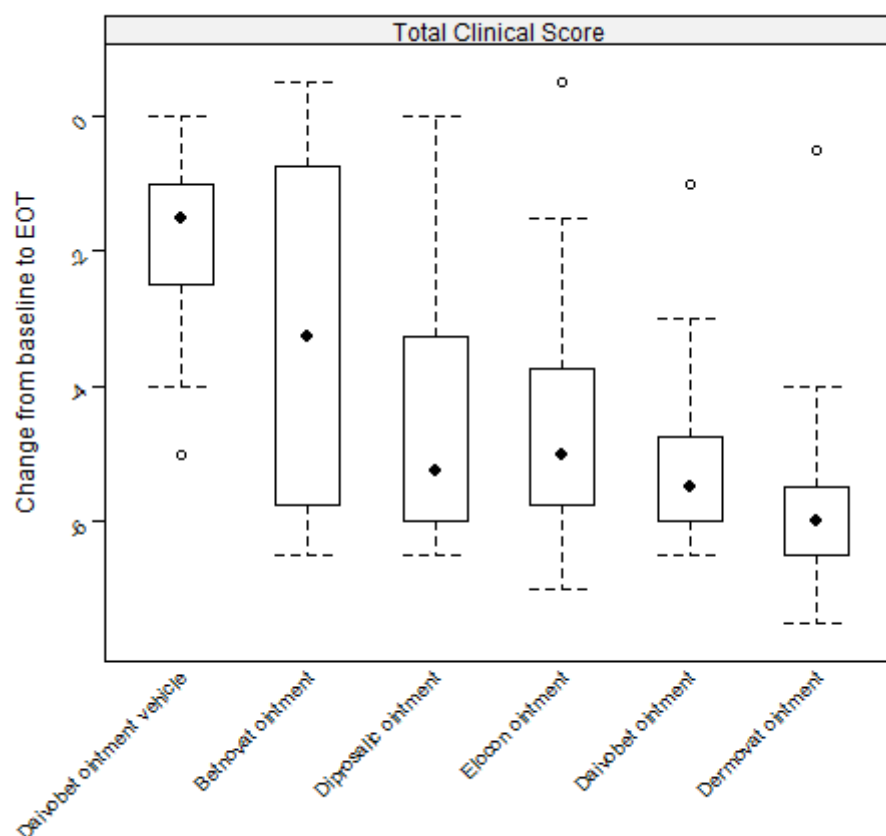
Subjects using biological therapies (marketed or not marketed) with a possible effect on psoriasis (e.g. alefacept, efalizumab, etanercept, infliximab, adalimumab) within 12 weeks prior to study drug administration

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<p>2. Systemic treatments with all other therapies than biologicals, with a potential effect on psoriasis vulgaris (e.g., corticosteroids, vitamin D-analogues, retinoids, immuno-suppressants) within the 4-week period prior to randomisation</p> <p>3. Subjects using one of the following topical drugs for the treatment of psoriasis within four (4) weeks prior to study drug administration</p> <ul style="list-style-type: none"> <li>- Potent or very potent (WHO group III-IV) corticosteroids</li> <li>- PUVA or Grenz ray therapy</li> </ul> <p>4. Subjects using one of the following topical drugs for the treatment of psoriasis within two (2) weeks prior to study drug administration: WHO group I-II corticosteroids; Topical retinoids; Vitamin D-analogues; Topical immunomodulators (e.g. macro-lides); Anthracen derivatives; Tar; Salicylic acid; UVB therapy</p> <p>5. Subjects with current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis</p> <p>6. Subjects with any of the following conditions present on the test area: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections and atrophic skin</p>		
<p>Investigational product, dose, method of administration, lot numbers:</p> <p><b>Investigational products:</b></p> <p>Daivobet® ointment, calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate). Diprosalic® ointment: betamethasone 0.5 mg/g (as dipropionate) plus salicylic acid 30 mg/g; Betnovat® ointment: betamethasone 1 mg/g (as valerate); Dermovat® ointment, clobetasol-17-propionate 0.5 mg/g; Elocon® ointment, mometasonefuroate 1mg/g</p> <p>Route of administration and dosage: Topical. Fifty (50) µl were applied per application and per site.</p>		
<p>Reference product, dose, method of administration, lot numbers:</p> <p><b>Reference products:</b></p> <p>Daivobet® ointment vehicle</p> <p>Route of administration and dosage: Topical. Fifty (50) µl were applied per site.</p>		

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Duration of treatment: The treatment phase was 20 days (18 applications)		
Criteria for evaluation Efficacy : The primary response criterion was the absolute change in TCS of clinical symptoms (sum of erythema, scaling and infiltration) at end of treatment compared to baseline. The secondary response criteria were; 1) absolute change in single clinical symptom score: Erythema, scaling, infiltration at end of treatment and individual visits compared to baseline, and 2) Change in Total Clinical Score (TCS) at individual visits compared to baseline, and 3) Change in lesion thickness measured by ultrasound at each assessment at day 8, 15, and 22 compared to baseline. Safety: Any reported adverse events (AEs) or adverse drug reactions (ADRs).		
Statistical methodology The primary variable was analysed by pair-wise, two-sided t-tests with 5% level of significance. Due to the explorative nature of the study, no correction for multiplicity was considered necessary, though multiplicity was addressed in a supplementary randomisation test. The absolute change in Total Clinical Score and its components from baseline to each assessment was tabulated by treatment. The absolute change from baseline to end of treatment of Skin Thickness was analysed by pair-wise, two-sided t-tests with 5% level of significance. The absolute change in Skin Thickness (mm) and its components from baseline to each assessment is tabulated by treatment.		
Summary – Conclusions Efficacy results: Treatment with a WHO group IV steroid product, Dermovat® ointment, and the combinational product, Daivobet® ointment (including a WHO group III steroid product), showed the largest change in TCS from baseline to end of treatment. Only Dermovat® ointment showed significantly better response rates than the remaining three group III steroid products, Diprosalic® ointment, Elocon® ointment and Betnovat® ointment. Daivobet® ointment		

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showed a statistically significant higher treatment response to only Betnovat® ointment, whereas no difference was shown when compared with Diprosalic ointment and Elocon® ointment. The significantly higher effect of Dermovat® ointment on the TCS was evident from day 11. The ointment vehicle had the smallest change in Total Clinical Score (TCS), which was significantly lower compared to all other products.



**Figure 1: Absolute change in TCS from baseline to end of treatment: randomised subjects**

The absolute change in TCS from baseline to end of treatment corresponded well with the

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<p>change in all three individual components, scaling, erythema and infiltration. Here, Dermovat® ointment showed the largest change, and Daivobet® ointment vehicle showed the smallest change, from baseline for scaling, infiltration and erythema.</p> <p>The results of the secondary response criteria: Ultrasound measurements, change from baseline of TCS by visit and of each component (scaling, erythema and thickness) by visit, corresponded well with the TCS for all products tested.</p>		
<p>Safety results: Two adverse events considered not related to the study medication were reported. There were no deaths or serious adverse events. Thus, no unexpected or significant safety issues were arising within the 3 weeks' treatment period.</p> <p>Conclusion: The aim of the study was to measure the relative difference in TCS between Daivobet® ointment and four steroid products in subjects with psoriasis vulgaris.</p> <p>The primary response criterion of the study was the absolute change in TCS of clinical symptoms. At end of treatment, efficacy of Daivobet® ointment was comparable to the effect of Dermovat® ointment, Diprosalic® ointment and Elocon® ointment, and statistically significant superior to Betnovat® ointment and the Daivobet® ointment vehicle.</p> <p>The change in ultrasound measurement and each individual component of TCS corresponded well with the change in TCS of the treated lesions.</p> <p>No serious adverse events were reported during the study.</p>		
Date of report: 15-SEP-2009		