SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	(For National Authority Use only)
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Title of study/Protocol Code Number:
A plaque test comparing three marketed products and two investigational products and a vehicle control for the treatment of psoriasis vulgaris / PLQ-001

Centre details:
Single centre in France

Publication references:
No publication planned

Study period details:	Phase of development:
The first subject enrolled on 25 Feb 2008	Phase II
The last subject completed study on 31 Mar 2008	

Objectives/hypothesis, if applicable:
To evaluate the psoriasis plaque test by comparing the efficacy of six different treatment products, and to validate the use of immunohistochemical and histological scoring of biopsy material in conjunction with clinical scoring of the treated plaques in the evaluation of treatment effects in psoriatic skin.

Study methodology:
The study was a single centre, investigator blinded, within-subject randomised, active- and vehicle-controlled, repeated dose, intra-individual comparison in subjects with psoriasis vulgaris.
All subjects received all study medications on different test sites.
The study consisted of a screening visit, a wash-out period if needed, a treatment period of 21 days. At the final treatment visit biopsies are taken and sutures are removed 10 days later. If applicable a follow-up visit was performed.

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Number of patients enrolled:

A total number of 27 subjects with stable psoriasis vulgaris were enrolled. 24 randomised subjects got all study medications.

Diagnosis and main criteria for patient selection:

Subjects of either sex, 18 years of age or above with a diagnosis of stable psoriasis vulgaris. Psoriasis vulgaris lesions (plaques) were located on arms, legs or trunk.

Subjects with psoriasis lesions (plaques) assessed by a Total Clinical Score (sum of scores of erythema, scaling and infiltration) of 4 to 9 inclusive but each individual item ≥ 1.

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

LEO 80185/Xamiol[®] gel, lot 062956101: combination of calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) in a gel vehicle.
LEO 80190 ointment, lot 0731661: combination of calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g in an ointment vehicle.
Topical application. 50μl was applied per application and per site once daily, 6 days a week (except Sundays).

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

Daivonex[®] ointment, lot 0732361 (calcipotriol 50 mcg/g)
Daivonex[®] cream, lot 0732362 (calcipotriol 50 mcg/g)
Daivobet[®] ointment, lot 0722861 (combination of calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate)
Daivobet[®] ointment vehicle, lot 0722761
Topical application. 50μl was applied per application and per site once daily, 6 days a week (except Sundays).

Duration of treatment:

Three weeks (18 applications) treatment.

Criteria for evaluation

Efficacy :

Primary response criteria:
Absolute change in Total Clinical Score (TCS) of clinical symptoms (sum of erythema, scaling and infiltration) at end of treatment compared to baseline.

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Secondary response criteria:

Clinical:

Absolute change in single clinical symptom score, i.e. erythema, scaling, infiltration compared to baseline.

Change in Total Clinical Score (TCS) at individual visits compared to baseline.

Ultrasound skin echography:

Lesion thickness measured by ultrasound.

Safety:

Incidence, duration and severity of adverse events.

Biomarkers:

Epidermal thickness, differentiation and proliferation, morphology and infiltration of inflammatory cells.

Safety:

Any adverse events reported.

Statistical methodology

The primary variable will be 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 is considered necessary.

The absolute change in Total Clinical Score and its components from baseline to each assessment will be tabulated by treatment.

The relation between, on the one hand, Total Clinical Score and its components (erythema, scaling and infiltration) and, on the other, the biomarkers will be explored using general linear models and multivariate analysis.

Summary - Conclusions

Efficacy results:

Primary response criterion:

Absolute change in Total clinical score and its components from baseline to end of treatment (visit day 22): randomised subjects.

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The development of TCS over time is displayed below.
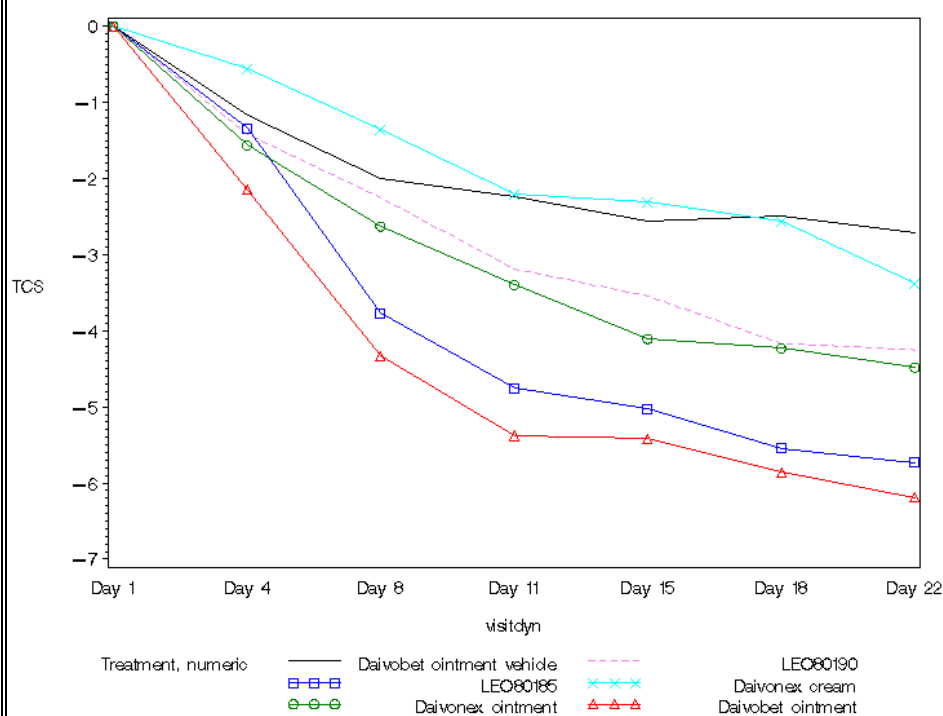
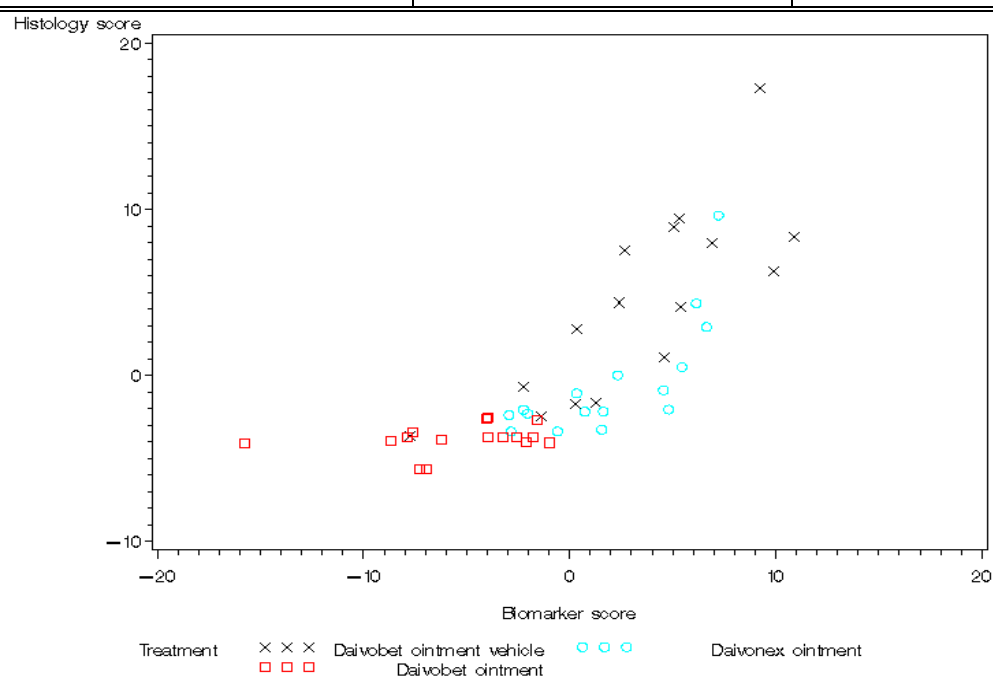*Absolute change in Total Clinical Score for the different treatments: randomised subject.*

The overall impression is that the six treatments divide into three pairs:

1) Daivobet® ointment and LEO 80185 which have the largest reductive and significant effect on TCS.
2) Daivonex® ointment and LEO 80190, which are less efficient than the pair in 1) but still more efficient than the two treatments below:
3) Daivobet® ointment vehicle and Daivonex® cream, the two treatments that have the least effect.

Secondary response criterion:
The effect of the Daivobet® ointment, Daivonex® and Daivobet® ointment vehicle when the biopsy endpoints are used to measure efficacy and to compare the biopsy endpoints to TCS as response variables.

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The Histology score versus the Biomarker score with treatment groups marked. The more efficient the product is the lower are the marker scores.

The results showed that both Daivonex® and Daivobet® ointment had a significant effect on histology and biomarkers compared to the ointment vehicle. However, the improved effect of Daivonex® ointment compared to the vehicle was only present for the histology but was not observed for the biomarkers.

In contrast, Daivobet® ointment had a significantly positive effect on all biomarkers analysed compared both to the vehicle and Daivonex® ointment. It indicates that Daivobet® ointment more strongly affects the morphology, infiltration and differentiation of the epidermis than the Daivonex® ointment. This finding corresponds well with previous results as well as with the results of the TCS in this study. In addition, these results suggest that calcipotriol (in Daivonex®), in contrast to steroids (in Daivobet®), primarily have effect on cell differentiation (strong effect on the morphology), and only modest effect on the inflammation in psoriasis, whereas the opposite is true for steroids. This confirms what is

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known from the literature.

The results also show a good correlation between the selected biomarkers and TCS in the psoriasis lesions. The most efficient treatment of psoriasis in this study, Daivobet® ointment, influenced a broad panel of biomarkers.

Safety results:

No serious adverse events were reported during the study.

Conclusion:

The aim of the study was to evaluate the use of the psoriasis plaque test study and specific selected biomarkers in predicting treatment efficacy of psoriasis vulgaris. The relative difference in TCS between the treatment compounds in the plaque test corresponded well to the difference in TCS between the previous larger clinical studies with the single compounds. This suggests that such plaque tests in the future could be used early in the development process to select a lead compound for full clinical development among a group of promising candidates.

The change in histological and immunohistochemical values corresponded with the change in TCS of the treated lesions. Therefore, those markers can not only predict TCS, but also explain why there is a difference in efficacy between products, and they can give new important information on the mode of action and mechanisms of the treatment products.

The primary response criterion of the study was the absolute change in TCS of clinical symptoms. Daivobet ointment and LEO 80185 gel showed a statistically significant difference in TCS at end of treatment compared to baseline confirming their superior efficacy to the other products.

No serious adverse events were reported during the study.

By combining clinical scoring and biomarker measurements a more accurate conclusion regarding treatment effects can be drawn from this study. Plaque test studies can therefore improve the prediction of treatment efficacy in regular clinical studies.

Report date:

18-MAR-2009