2 SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S
Name of Finished Product: **Dairovobet/Dovobet** Ointment
Name of Active Ingredients:
Calcipotriol
Betamethasone dipropionate

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**Title of Study:** Dairovobet/Dovobet ointment / UV penetration study in humans - Detection of erythema induced by UV light, within subject comparison of investigational materials against untreated skin

**Clinical Investigator:** [BSc MBChB MRCP FFPM]

**Study Centre:** Scotland

**Publication Reference:** To be decided.

**Studied Period:** 05-Dec-2003 to 19-Dec-2003

**Phase of Development:** Phase 1

**Objectives:**
To evaluate the ultraviolet (UV) light penetration potential of Dairovobet/Dovobet ointment, Dairovobet/Dovobet ointment vehicle, Dairovonex/Dovonex scalp solution and Dairovonex/Dovonex scalp solution vehicle. A standard sunscreen and a standard emollient were also included.

**Methodology:** The study was a single centre, randomised, double-blind, active and vehicle controlled, within subject comparison study. Subjects were screened for inclusion in the study before Day 1 and entered the test centre on Day 1 for determination of the minimal erythema dose of untreated skin (MED (US)). Each subject was administered an ascending series of 8 UV light exposures (0.6 min, 0.8 min, 1.0 min, 1.2 min, 1.5 min, 1.9 min, 2.4 min and 3.0 min) within a 50 cm² test site on the back. Skin reactions were assessed immediately after exposure and erythema was assessed on the subject’s return to the test centre 23 h (± 1 h) after exposure (Day 2). Seven further 50 cm² test sites were delineated on each subject’s back, one each for Dairovobet/Dovobet ointment, Dairovobet/Dovobet ointment vehicle, Dairovonex/Dovonex scalp solution and Dairovonex/Dovonex scalp solution vehicle, a standard sunscreen, a standard emollient and untreated skin (for evaluation of a repeat MED (US)), according to a randomisation schedule. Each of these 7 sites was divided into 8 sub sites and was exposed to an incremental range of 8 UV doses, based on individual pre-treatment MED (US) results from the Day 1 UV exposure. Skin reactions were assessed immediately after exposure and erythema was assessed on the subject’s return to the test centre 23 h (± 1 h) after exposure (Day 3). Adverse events were recorded throughout the study.

**Number of Subjects (planned and analysed):** It was planned that 25 subjects would enter the study to provide at least 20 subjects with valid data for analysis. Twenty-five (25) subjects entered the study and received the Day 1 UV exposure. MED (US) could...
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not be determined for 2 subjects and they were withdrawn, leaving 23 subjects who completed the study.

**Diagnosis and Main Criteria for Inclusion:** Healthy male or female subjects, 18 to 55 years of age and with a Fitzpatrick skin type I to III.

**Test Products, Doses, Modes of Administration and Lot Numbers:**
Daivobet/Dovobet ointment (lot number [redacted]), Daivonex/Dovonex scalp solution (lot number [redacted]), Daivobet/Dovobet ointment vehicle (lot number [redacted]) and Daivonex/Dovonex scalp solution vehicle (lot number [redacted]) were each applied topically to 50 cm² test sites at a dose of 2 mg/cm² per site.

**Duration of Treatment:** Each test material was spread evenly over a test site and was left for 15 min before UV light exposure. Each test site was exposed to an incremental range of 8 UV doses, based on MED (US) results for each subject and evaluations were performed the following day.

**Reference Therapies, Doses, Modes of Administration and Lot/Batch Numbers:**
Standard sunscreen 8% homosalate (batch number [redacted]) and standard emollient, Diprobase Cream (batch number [redacted]), were each applied topically to 50 cm² test sites at a dose of 2 mg/cm² per site.

**Criteria for Evaluation**

**UV Penetration:** UV penetration was assessed using erythema scores (clinical assessments of erythema on a 5-point scale from 0 to 4) from the 8 test sites, recorded at 23 h (± 1) h after Day 1 and Day 2 UV exposure. Erythema scores were used to calculate the MED (US), repeat MED (US) and MED treated skin (TS) for each test material and each subject. The sun protection factor (SPF) for each test material was determined using the repeat MED (US) and MED (TS). Immediate skin responses to UV exposure were evaluated and graded as independent responses as follows: oedema, spreading reaction, reaction to adhesive tape, immediate reddening, immediate pigment darkening.

**Safety:** Safety was assessed by examination of adverse events.

**Statistical Methods:** SPF was calculated for each of the 6 investigational materials using the formula MED (TS) / repeat MED (US), and was summarised including 95% confidence intervals. MED (US), repeat MED (US) and MED (TS) were summarised. Immediate responses to UV exposure and erythema scores recorded at 23 h (± 1) h after UV exposure were summarised. Adverse events were summarised.

**Summary – Conclusions**

**UV Penetration:** Mean SPF results for Daivobet/Dovobet ointment,
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| **Dairovbet/Doovobet** ointment vehicle, **Daivonex/Dovonex** scalp solution, **Daivonex/Dovonex** scalp solution vehicle and a standard emollient, Diprobease Cream, were broadly similar (0.98 to 1.18), and the 95% CI for each material contained the value 1 (the SPF for untreated skin). Therefore, there was no measurable change in UV penetration, determined by SPF calculation, after application of any of the investigational materials (active or vehicle).

The mean SPF of the standard sunscreen was calculated to be 3.06 (95% CI 2.58 to 3.54). This was outwith the expected range (4.47 ± 1.279). However, this was not considered to affect the integrity of the results.

There was some evidence of an increase in immediate skin responses to UV exposure with longer UV exposures. The numbers of subjects with a recorded response were broadly similar for all the investigational materials, except the standard emollient for which no immediate responses were recorded.

**Safety:** No serious adverse events were recorded during the study and no subject was withdrawn from the study as a result of an adverse event. No adverse events were recorded for any subject after application of any of the 6 investigational materials.

**Conclusion:** There was no measurable increase in UV penetration, determined by SPF calculation, after application of any of the investigational materials. Therefore, it can be concluded that application of investigational materials did not induce further UV penetration in comparison with untreated skin. The mean SPF for the 8% homosalate standard sunscreen was lower than expected in the protocol but did demonstrate protection to UV. The standard emollient demonstrated similar values to the investigational materials (95% CI contained the value 1) and as such demonstrated the validity of the study. There was some evidence of an increase in immediate skin responses (immediate pigment darkening) with longer UV exposures. All products showed a good safety profile, with no adverse events being recorded by any subject after application of any of the 6 investigational materials.