Clinical Study Report

Daivobet/Dovobet Ointment / UV Penetration Study in Humans - Detection of Erythema Induced by UV light, A Within Subject Comparison of Investigational Materials Against Untreated Skin

Authors: 

Sponsor: 
LEO Laboratories Ltd
Longwick Road
Princes Risborough
Buckinghamshire
HP27 9RR, UK

Contract Research Organisation: 

Scotland

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information. Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered. Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient and Scientific Review Board. Appendices to the clinical study report are omitted. Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA.
Sponsor Signature Page

For approval of the signed clinical study report for the following study:

Daivobet/Dovobet Ointment / UV Penetration Study in Humans - Detection of Erythema Induced by UV light, A Within Subject Comparison of Investigational Materials Against Untreated Skin

Sponsor:
LEO Laboratories Ltd
Longwick Road
Princes Risborough
Buckinghamshire
HP27 9RR, UK

Contract Research Organisation:

Sponsor Code: MCB 0306 UK
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18-JUN-2004

Date
17-JUN-2004

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1 TITLE PAGE

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<td>Clinical Investigator/Affiliation:</td>
<td>___ BSc MBChB MRCGP FFPM, ___</td>
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Copies of case report forms (CRFs), study documentation and a copy of the final report will be stored in the archives of ____. All data will be retained according to ICH guidelines. After 5 years the sponsor will be consulted regarding their disposition or continued storage.

The trial was conducted in accordance with the Guidelines for Good Clinical Practice and the ICH Guidelines approved by CPMP in July 1996 (CPMP/ICH/135/95).

Daivobet/Dovobet and Daivonex/Dovonex are trademarks used by LEO Pharma A/S (or its subsidiaries).
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<td>Number of Subjects (planned and analysed):</td>
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Individual Study Table

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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,
Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle and a standard emollient, Diprobase 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.
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4 LIST OF ABBREVIATIONS

% = percent
AE = adverse event
CI = confidence interval
cm = centimetre
CRF = case report form
CRO = contract research organisation
EU = European Union
FDA = Food and Drug Administration
g = gram
GCP = Good Clinical Practice
GP = General Practitioner
h = hour
ICH = International Conference on Harmonisation
IPD = immediate pigment darkening
MED = minimal erythema dose
MedDRA = Medical Dictionary for Regulatory Activities
MED (TS) = minimal erythema dose (treated skin)
MED (US) = minimal erythema dose (untreated skin)
mg = milligram
min = minute
NDA = New Drug Application
SAE = serious adverse event
SD = standard deviation
SPF = sun protection factor
WHO = World Health Organisation
WMA = World Medical Association
UK = United Kingdom
USA = United States of America
UV = ultra violet
5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE
The final protocol, the volunteer information and the consent form were submitted to the Independent Ethics Committee of [Redacted] for consideration. The committee met on 02-Dec-2003 and requested minor changes to the protocol and volunteer information. These changes were addressed in Protocol Amendment 1, dated 03-Dec-2003 (Appendix I) and a revised volunteer information and were approved by the Chairman of the Ethics Committee on 05-Dec-2003 (Appendix III).

5.2 ETHICAL CONDUCT OF THE STUDY
The study was performed in accordance with Good Clinical Practice (GCP) and with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland (1964) as amended by the 29th WMA General Assembly, Tokyo, Japan (1975), the 35th WMA General Assembly, Venice, Italy (1983), the 41st WMA General Assembly, Hong Kong (1989), the 48th WMA General Assembly, Somerset West, Republic of South Africa (1996) and the 52nd WMA General Assembly, Edinburgh, Scotland (2000) revisions.

5.3 VOLUNTEER INFORMATION AND CONSENT
At screening each volunteer was informed of the nature and risks of the study and was given a copy of the consent form and volunteer information to review and sign before any study related activity was carried out. An example of the volunteer information and informed consent can be found in Appendix A of the protocol, Appendix I. Each volunteer’s General Practitioner (GP) was informed of their patient’s participation before the start of the study.

The volunteers were asked to consent that data were recorded, collected, processed and could be transferred (to European Union (EU) and non-EU countries), in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).
6 INVESTIGATORS, STUDY ADMINISTRATIVE STRUCTURE, INSURANCE AND LIABILITY

6.1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This clinical trial was performed by a contract research organisation (CRO), on behalf of LEO Laboratories Ltd. The management of the study was the responsibility of The clinical investigator was BSc MBChB MRCGP FFPM. The declaration of the clinical investigator is given in Appendix V.

The sponsor provided Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution and Daivonex/Dovonex scalp solution vehicle. supplied the standard sunscreen, 8% homosalate, and the standard emollient, Diprobase Cream.

Quality assurance, data management, data reporting and medical writing were performed by The Consultant Dermatologist was MBBS MRCP DCH AFOM FRCP.

Full details of the clinical investigator and other study personnel are given in Appendix IV.

6.2 INSURANCE AND LIABILITY

The subjects in the study were covered by the product and general liability insurance of LEO or LEO itself in the event of trial related injury or death, in accordance with applicable law and with the CPMP Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) of 17-Jul-1996.
7 INTRODUCTION

Daivobet (also named Dovobet) ointment contains calcipotriol 50 μg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate). In the formulation of Daivobet/Dovobet, betamethasone dipropionate was chosen as the corticosteroid because of its widespread use throughout the world and because of its higher stability compared with other betamethasone compounds. Calcipotriol and betamethasone dipropionate are both well known drugs which have been in clinical use for several years.

Eight Phase I studies with Daivobet/Dovobet ointment in healthy volunteers have been completed. The efficacy and safety of Daivobet/Dovobet ointment in patients with psoriasis vulgaris has been investigated in 6 Phase III studies. The Daivobet/Dovobet trial programme, including more than 2500 patients treated with Daivobet once or twice daily, showed that approximately 10% of patients can be expected to experience a non-serious adverse reaction. The common adverse reactions are pruritus, skin rashes and a burning sensation.

Daivonex/Dovonex scalp solution contains calcipotriol 50 μg/g (as hydrate).

This study was conducted to investigate if the 2 drugs (Daivobet/Dovobet ointment and Daivonex/Dovonex scalp solution) or either of their vehicles (ointment or solution) could modify (enhance) the sensitivity of skin to ultraviolet (UV) radiation. It was considered more relevant to investigate the UV penetration enhancing effect in human volunteers instead of in animals to avoid uncertainties in the extrapolation from animal results to human conditions.

The information to be gained from this study has been requested by the United States of America (USA) Food and Drug Administration (FDA) as part of the documentation to be submitted in a New Drug Application (NDA) file for Daivobet/Dovobet ointment in the USA.
8 STUDY OBJECTIVES

This study was designed to evaluate the UV penetration of investigational materials and their vehicles (placebo). It is known that the investigational test and placebo materials do not contain sunscreens but it may be that the investigational materials elicit greater UV light penetration (higher erythema scores) compared with an untreated test site. A standard emollient (Diprobase Cream) was included in the study to demonstrate the UV penetration of a ‘standard’ moisturiser. A standard sunscreen (8% homosalate) was also included to validate the evaluation of erythema and SPF (assay sensitivity).
9 INVESTIGATIONAL PLAN

9.1 STUDY DESIGN AND PLAN – DESCRIPTION AND RATIONALE

This was a randomised, double-blind, active and vehicle controlled, within subject comparison study.

On Day 1, subjects were administered an incremental geometric series of 8 UV light exposures within a 50 cm² test area of untreated skin (US) on their backs. Skin reactions were assessed immediately after UV exposure and erythema was assessed 23 h (± 1 h) after UV exposure. Erythema scores at each exposure time were used to determine each subject’s minimal erythema dose of untreated skin (MED (US)).

On Day 2, 7 further 50 cm² test sites were each exposed to an incremental series of 8 UV light exposures, with the length of exposure derived from the MED (US) calculated from the Day 1 UV exposure. One of the 7 test sites was a second area of untreated skin. Erythema scores (23 h (± 1 h) after UV exposure) from this site were used to derive a second (repeat) MED (US) that was used to calculate the sun protection factor (SPF) for the investigational materials. The remaining 6 test sites were used for Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, a standard sunscreen and a standard emollient. Each test material was spread evenly over a test site at a dose of 2 mg/cm² per site and was left for 15 min before UV light exposure. Skin reactions were assessed immediately after UV exposure and erythema was assessed 23 h (± 1 h) after UV exposure. Erythema scores were used to determine each subject’s minimal erythema dose of treated skin (MED (TS)). Adverse events were recorded throughout the study.

The entire study protocol is presented in Appendix I and the unique pages of the CRF are presented in Appendix II.

9.1.1 Dosing Schedule

All subjects received a single dose of 0.1 g of Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, a standard sunscreen (8% homosalate) and a standard emollient on Day 2 of the study.
9.1.2 Study Sequence

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<td>Application of investigational materials</td>
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<td>Irradiation of treated and untreated skin</td>
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<td>Erythema scores and determination of MED (TS) and repeat MED (US)</td>
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9.2 RATIONALE OF THE STUDY DESIGN

Although a potential UV penetration enhancing effect could have been investigated in hairless mice or another animal species, it was considered more relevant to investigate this directly in human volunteers to avoid uncertainties in the extrapolation from animal results to human conditions.

Because the study was investigating UV light penetration, even though the active test materials and their vehicles do not contain sunscreens, the test methodology applied in this study generally conformed to the SPF Test Method outlined by the USA FDA Guideline For Sunscreen Products For Over-The-Counter Human Use (2).

It was necessary to include both the active test materials and their vehicles in this study as either could have demonstrated an enhancing effect on the UV skin penetration and any effect of the Daivobet/Dovobet ointment could have been masked by the presence of betamethasone dipropionate.

The effect of the 2 active test materials and the 2 vehicles on the UV skin penetration was compared with an untreated area and with an 8% homosalate standard sunscreen. In addition, a standard emollient was included in the trial to allow the UV penetration
with the investigational materials to be compared with the UV penetration of a commercially available 'standard' emollient.

9.3 SELECTION OF STUDY POPULATION

Subjects were healthy male and female volunteers aged 18 to 55 years and with a Fitzpatrick skin type I to III (1), selected from the panel of volunteers recruited by Twenty-five subjects were to enter the study to produce valid data from at least 20 subjects for the standard sunscreen. Subjects were screened for inclusion in the study before the first UV exposure (Day 1).

9.3.1 Inclusion Criteria

a) Age 18 to 55, either sex.
b) Able to communicate well with the investigator and to comply with the requirements of the entire study.
c) Provision of written informed consent to participate as shown by a witnessed signature on the volunteer consent form.
d) A Fitzpatrick skin type I to III.
e) Adequate methods of contraception, including condoms with spermicide gel, diaphragm with spermicide gel, coil (intra-uterine device), surgical sterilisation, vasectomy, oral contraceptive pill, depo-progestogen injection and abstinence.

9.3.2 Exclusion Criteria

a) Females who were pregnant or breast feeding or became pregnant during the study.
b) Those suffering from any active skin disorders.
c) Those taking medications which in the opinion of the clinical investigator might affect test results, for example anti-inflammatory immunosuppressive drugs, essential oils, or drugs which could cause photosensitivity.
d) Those with sunburn, suntan, scars, tattoos, and uneven skin tones on the test sites.
e) Those with nevi, blemishes, or moles on the test sites, that in the physician's judgement would interfere with the study results.
f) Those suffering from any medical condition, which in the opinion of the clinical investigator would automatically exclude them from participating in the study.
g) Fitzpatrick skin types IV to VI.
h) Sunbathing or use of sun lamp and solaria within the previous 4 weeks.
i) Those with a history (within the last year) of photosensitivity.
j) Those with a history (within the last year) of drug or alcohol abuse.
k) Those who had participated in a similar study within the previous 4 weeks.
l) Administration of any investigational drug within the previous 3 months (or within the previous 4 months if the drug was a new chemical entity).
m) Those previously enrolled/randomised in this trial.
n) Those with known or suspected hypersensitivity to component(s) of the investigational products.

9.3.3 Pre-study Screening

The screening procedure consisted of the following:

- Consent procedure (Appendix A of Protocol Amendment 1, Appendix I).
- Completion of Supplementary Health Questionnaire for Volunteers on Photostudies (Appendix B of Protocol Amendment 1, Appendix I).
- Completion of Questionnaire for Test Participation (Appendix C of Protocol Amendment 1, Appendix I).
- Review of health questionnaire and inclusion/exclusion criteria by test personnel.
- Pregnancy testing of women of child-bearing potential (on-site urine pregnancy test).
- Review for inclusion and inspection of back by Consultant Dermatologist.

A pre-test examination of each subject’s back was performed on Day 1 to determine the presence of sunburn, suntan, scars, active dermal lesions and uneven skin tones. If, in the opinion of the Consultant Dermatologist, any of the findings of this examination were significantly outside what could be expected in a ‘normal’ individual, the subject was excluded from the study. The presence of nevi, blemishes or moles was acceptable if, in the opinion of the Consultant Dermatologist, they would not interfere with the study results. Any excess hair on the back was clipped in order not to interfere with study results, or if this was not possible the subject was excluded from the study.

9.3.4 Restrictions

Subjects should shield their back from UV light during the course of the study. Subjects must only take paracetamol should they require pain-killers. Subjects were able to leave the test facility after each appointment.

9.3.5 Removal of Subjects from Therapy or Assessment

If a subject wished to leave the study at any time they were permitted to do so. Reasonable efforts were to be made by [redacted] to determine the reasons for withdrawal.

A subject could be withdrawn from the study in any of the following circumstances:

a) Serious or severe adverse events.
b) Major violation of the protocol.
c) Withdrawal of consent.
d) Termination of the study by the sponsor.
9.4 TREATMENTS

9.4.1 Treatment Administered

On Day 1, all subjects received a series of 8 UV light exposures within a 50 cm² test area on the back. The test site was marked out on the back between the belt line and the scapula region and lateral to the midline. This was done using a light-proof template with 8 subsites secured with Blenderm tape (or micropore tape if any irritation was experienced with the Blenderm tape). The time intervals of UV exposure selected were a geometric series approximately 25% greater than the previous exposure time (0.6, 0.8, 1.0, 1.2, 1.5, 1.9, 2.4 and 3.0 min). Additional times, up to a maximum of 3.7 min could be included if required. The erythema reaction to these UV exposures was used to calculate MED (US). This was used to determine the UV exposure times after administration of the investigational materials on Day 2. Details of the UV radiation source, the radiometer used to measure intensity and the measurement of uniformity of UV intensity can be found in Sections 8.1, 8.2 and 8.3 of Protocol Amendment 1 (Appendix I).

On Day 2, all subjects received a single dose of 0.1 g of Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, a standard sunscreen and a standard emollient. Each dose was applied using a syringe and spread over the test area using a gloved finger to achieve an even film. Each was applied to one of 7 50 cm² test sites according to the randomisation schedule provided by the sponsor. All treatments were left on the skin for 15 min before UV light exposure. One of the 7 test sites was left as untreated skin (also allocated according to the randomisation schedule).

All subjects received a series of 8 UV light exposures to each of the 4 test sites to which test material had been applied (Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle) and to the test site with a standard emollient. The time intervals of UV exposure were a geometric series based on the MED (US) established on Day 1, as follows:

MED (US) × 1.25⁻⁴, MED (US) × 1.25⁻³, MED (US) × 1.25⁻², MED (US) × 1.25⁻¹, MED (US), MED (US) × 1.25, MED (US) × 1.25², MED (US) × 1.25³

The test site containing the standard sunscreen received a series of 8 UV light exposures based on an incremental 1.25 geometric progression between each successive UV dose. The MED (US) was multiplied by the expected SPF of the material (SPF 4) giving an exposure time in minutes.

The final test site (untreated skin) received the same series of UV exposures used on Day 1 to enable a second (repeat) MED (US) to be established (additional times up to
3.7 min could be added if required at the discretion of test personnel. This repeat MED (US) was used, along with the MED (TS) results, to calculate the SPF for the 6 test sites treated with Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, the standard sunscreen and the standard emollient.

Subjects were requested to shield their backs from UV radiation for a further 23 h (± 1 h).

9.4.2 Identity of Investigational Products
The active ingredients of Daivobet/Dovobet ointment were calcipotriol (as hydrate) 50 μg/g and betamethasone (as dipropionate) 0.5 mg/g. The active ingredient of Daivonex/Dovonex scalp solution was calcipotriol (as hydrate) 50 μg/g.

The active test materials and their vehicles were provided by the sponsor. Daivobet/Dovobet ointment and Daivobet/Dovobet ointment vehicle were packed in tubes, and Daivonex/Dovonex scalp solution and Daivonex/Dovonex scalp solution vehicle were packed in bottles. The standard emollient, Diprobase Cream, was provided by and was stored below 25°C. The standard sunscreen, 8% homosalate, was manufactured by and stored at + 4°C ± 2°C.

Supplies of Daivobet/Dovobet ointment (lot number , expiry date Apr-2004), Daivobet/Dovobet ointment vehicle (lot number , expiry date Feb-2005), Daivonex/Dovonex scalp solution (lot number , expiry date Jun-2005), Daivonex/Dovonex scalp solution vehicle (lot number , expiry date Oct-2005) were received on 12-Dec-2003 and were stored at below 25°C (ambient temperature).

Standard sunscreen, 8% homosalate (batch number , expiry date 09-Jul-2004), and standard emollient, Diprobase Cream (batch number , expiry date May-2008) were received on 23-Jul-2003 and 15-Dec-2003, respectively, and were stored as detailed above.

An accountability record of utilisation was maintained throughout the study. Unused active test materials and their vehicles were returned to the sponsor. Details of materials used are given in Appendix VI.

9.4.3 Method of Assigning Subjects to Treatment Groups
A subject number was assigned to all subjects who qualified for the study in accordance with the inclusion and exclusion criteria. The number assigned was the lowest number available. Subject numbers were allocated according to the code to .
The allocation of investigational materials and untreated skin to each of the 8 test sites for each subject was based on a randomisation code supplied by the sponsor (Appendix VII).

### 9.4.4 Selection of Doses in the Study

Investigational materials (Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution, standard sunscreen, 8% homosalate, and standard emollient, Diprobase Cream) were each applied at an amount of $2.0 \pm 0.04 \text{ mg/cm}^2$, giving a total of 0.1 g of material spread evenly over a 50 cm$^2$ test site. This dose reflected the application amount required by the FDA (2).

### 9.4.5 Selection and Timing of Dose for Each Subject

All subjects received a single dose of each of 6 investigational materials, Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, standard sunscreen, 8% homosalate, and standard emollient, Diprobase Cream.

Investigational materials were applied on Day 2 of the study and were left on the skin for 15 min before UV light exposure.

### 9.4.6 Blinding

This was a double-blind study. The allocation of investigational materials (and untreated skin) to the test sites was not divulged to the assessors conducting the assessments on Day 3. The application of test material to the test sites, irradiation and the immediate skin reaction assessments and scoring were performed by a technician who was blinded to Daivobet/Dovobet ointment vs Daivobet/Dovobet ointment vehicle, and blinded to Daivonex/Dovonex scalp solution vs Daivonex/Dovonex scalp solution vehicle.

The technician was not blinded to the location of the standard sunscreen (as this was to receive a longer UV exposure than the other sites), the standard emollient, or the Day 1 and Day 2 untreated areas.

The sponsor supplied Daivobet/Dovobet ointment and Daivobet/Dovobet ointment vehicle blinded, and supplied Daivonex/Dovonex scalp solution and Daivonex/Dovonex scalp solution vehicle blinded. The standard sunscreen and standard emollient were applied in an open manner.

No copies of the randomisation code were held by [censored] Medical Data Sciences Department during the clinical phase of the study.

Sealed treatment code envelopes, containing the identity of the investigational products, were provided to [censored] by the sponsor. These envelopes were held at the test facility.
The code was only to be broken in an emergency requiring investigational product identification. All treatment code envelopes were accounted for and returned to the sponsor before unblinding of the study.

The study was unblinded when a final validated database had been produced, when all treatment code envelopes had been accounted for and when a blinded review of the collected data had been performed.

9.4.7 Concomitant Therapy
No medications were permitted during the study except paracetamol or other drugs to treat minor conditions and those deemed necessary by the clinical investigator or supervising physician to treat adverse events. All medication taken was recorded in the case report forms (CRFs).

9.4.8 Treatment Compliance
Subjects were under supervision whilst in the test facility. Treatment application was performed by a technician and supervised by appropriately qualified personnel.

The use of all study treatments was recorded and an accountability record of utilisation was maintained. All deviations from the protocol were recorded.

9.5 CRITERIA FOR UV PENETRATION AND SAFETY

9.5.1 UV Penetration, Safety Measurements Assessed and Flow Chart

9.5.1.1 UV Penetration
UV penetration was assessed primarily using the erythema scores and exposure times from Day 3. A secondary assessment was made using the immediate responses recorded on Day 2.

The test sites were assessed for erythema by 2 independent technicians who did not administer the UV radiation or investigational materials 23 h (± 1 h) after irradiation on Days 2 and 3. Test sites were scored as follows:

0 = no visible reaction.
1 = slight but unambiguous erythema over the entire irradiation site with clearly defined borders.
2 = distinct unambiguous erythema over the entire irradiation site with clearly defined borders.
3 = intense erythema.
4 = visible, non-erythemal reaction (tanning).
MED was defined as the lowest UV exposure time that gave an erythema score of 1. The test sites were assessed immediately after irradiation by the technician carrying out the UV radiation procedure on Days 1 and 2 and scored (if present) as follows:

- **E** = oedema.
- **S** = spreading reaction outwith the irradiation site.
- **A** = marked reaction to the adhesive tape used to delineate the test site and secure the template.
- **R** = immediate reddening
- **IPD** = immediate pigment darkening.

### 9.5.1.2 Safety Measurements Assessed

#### 9.5.1.2.1 Adverse Events (AEs)

An AE was defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. At all visits after the start of treatment, the subject was asked a non-leading question to establish if any AEs had occurred. All AEs were recorded on the CRF with details of the event’s nature, intensity, duration, location (for cutaneous adverse events), suspected causal relationship to the investigational product, and the outcome.

The nature of the event was described in precise, standard medical terminology and a specific diagnosis given, if known. The intensity of the event was described as mild, moderate or severe according the investigator’s clinical judgement. A mild AE was an event that did not interfere in a significant manner with the subject’s normal functioning level. A moderate AE was an event that produced some impairment of functioning but was not hazardous to health. A severe AE was an event that produced significant impairment of functioning or incapacitation and/or was hazardous to the subject. The duration of the event was described by the start and end dates. The location for cutaneous adverse events could be described as either the face, scalp or trunk/limbs, and further described in terms of lesional/perilesional (2 cm or less from the border of lesion(s) treated with investigational product) or distant (more than 2 cm from the lesional border). The causal relationship of the AE to the use of the investigational product was described in terms of probable, possible, not related or not assessable according to the investigator’s clinical judgement. The outcome of the event was described as recovered/resolved, recovering/resolving, not recovered/not resolved, recovered with sequelae/resolved with sequelae, fatal or unknown.
9.5.1.2.2 Serious Adverse Events (SAEs)

An SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalisation or prolonged existing hospitalisation, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect, or other medically important condition according to the investigator’s clinical judgement. All SAEs (whether or not related to the investigational product or trial procedures) were to be reported to the sponsor within one working day of first knowledge by the investigator, and notified to the Independent Ethics Committee and National Health Authorities in writing according to local requirements. All SAEs were also to be recorded on the AE pages of the CRF. SAEs were to be followed until final outcome.

A pregnancy occurring during the trial was to be reported to the sponsor by use of the LEO Serious Adverse Event (SAE) Form – Clinical Trial and was to be handled as an SAE with regard to reporting time frame. Any pregnancies were to be followed until conclusion.
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Screening</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical/Surgical/Dermatological History</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test (women of child-bearing potential)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inspection of back by consultant dermatologist</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>UV exposure</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Immediate assessment of local responses to UV exposure</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Erythema scoring and determination of first MED (US)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Application of test material</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Erythema scoring and determination of second (repeat) MED (US)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Erythema scoring and determination of MED (TS)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Note:

- The first MED (US) was based on erythema scores 23 h (± 1 h) after Day 1 UV exposure and used to determine the length of UV exposures for each subject on Day 2.
- The second (repeat) MED (US) was based on erythema scores 23 h (± 1 h) after Day 2 UV exposure and used to determine the SPF for the 6 test materials.
- MED (TS) was based on erythema scores 23 h (± 1 h) after Day 2 UV exposure.
9.5.2 Appropriateness of Measurements
The nature and timing of assessments were considered appropriate by the clinical investigator to assess the UV penetration of the investigational materials and to evaluate safety.

9.5.3 Primary Endpoint and Secondary Endpoints
The primary endpoint of the study was the erythema scores recorded 23 h ± 1 h after Day 2 UV exposure. The secondary endpoint was the skin responses recorded immediately after the Day 2 UV exposure.

9.6 QUALITY CONTROL/QUALITY ASSURANCE
Quality control procedures in place at [redacted] were implemented to ensure data recorded in the CRFs were accurate before CRFs were sent for data entry purposes.

Quality assurance audits were carried out during the clinical and reporting phases of the study. Phases selected for audit could include, but were not limited to: protocol compliance, CRF data review, data, draft report and final report.

These audits were carried out according to standard operating procedures by Quality Assurance personnel independent of the staff involved in the study. Records of these audits were documented and distributed to senior management for review. The Quality Assurance statement is included in Appendix VIII.

In addition, the study was monitored by the Sponsor. A pre-study visit was made prior to the clinical phase to monitor the facilities. After the clinical phase a monitoring visit/endpoint of study visit was performed.

9.7 DATA MANAGEMENT AND STATISTICAL METHODS
9.7.1 Data Management Methods
Data management was performed by the Medical Data Sciences Department at [redacted]

Adverse events and medications were coded using MedDRA (v6.0) and the WHO Drug Reference List (2002) respectively. Independent coding reviews were performed within [redacted] and also by the sponsor.

All study data recorded in the CRF were subjected to interactive, double data entry using a validated database created in Clintrial (v4.3), a clinical data management system. Following data verification (completion of second entry), the audit trail was switched on, i.e. a computerised log of all subsequent changes to the data was recorded and the data were subjected to data consistency and validation checks. The resulting output was used to
raise queries after reference to the CRFs. All queries were raised using Data Query Forms (DQFs) and resolved with the assistance of [redacted] clinical staff.

On resolution of all data queries, the database was locked and all study data were exported to SAS (v8.2) for the production of data listings and summary tables.

All data listings for inclusion into the study report, except adverse events, were subjected to 10% quality control checks against the CRFs. All adverse events listings and summary tables were subjected to 100% quality control checks.

9.7.2 Statistical and Analytical Plans
The Medical Data Sciences Department at [redacted] produced all summary tables and data listings, using the statistical package SAS (v8.2)

In general terms, categorical data were presented using counts and percentages, whilst continuous variables were presented using the mean, median, standard deviation, minimum, maximum and number of subjects. In general, minima and maxima were quoted to the number of decimal places as recorded in the CRF; means, medians and standard deviations were quoted to one further decimal place. Percentages were rounded to one decimal place.

No interim analysis was performed for this study. All individual subject data were listed.

9.7.2.1 Demographics and Other Baseline Characteristics
The following demographic variables were summarised: age, sex and race. No significance testing of demographic data was performed. All individual subject details were listed.

Medical/surgical histories, medical/dermatological histories and medications taken at screening and during the study were listed including comments and coded fields.

Pregnancy test details and subject eligibility to continue in the study were listed for each subject.

9.7.2.2 UV Penetration
UV penetration was assessed primarily using the erythema scores and exposure times from Day 3. MED was defined as the lowest UV exposure time that gave an erythema score of 1. A secondary assessment was made using the immediate skin responses at the test sites recorded after irradiation on Day 2.

Erythema scores and immediate skin responses for treated and untreated skin were summarised and listed for each subject.
9.7.2.2.1 Determination of Sun Protection Factor (SPF)

SPF was calculated for each investigational material and for the standard sunscreen and emollient using the following formula:

\[
\text{SPF} = \frac{\text{MED (TS)}}{\text{Repeat MED (US)}}
\]

where MED (TS) was the minimal erythema dose for treated skin after application of 2 mg/cm² of the 6 investigational materials and repeat MED (US) was the Day 2 minimal erythema dose for untreated skin, ie skin to which no investigational product was applied. In effect, the SPF value is the reciprocal of the effective transmission of the product viewed as a UV radiation filter.

For the analysis of the investigational materials and the standard emollient, if erythema was present on all sites it was to be assumed that there was no erythema on the next lowest exposure time (ie assumed the lowest time divided by 1.25). Similarly, if erythema was absent on all sites it was to be assumed that erythema was present on the next highest exposure time (ie assumed the highest time multiplied by 1.25). All assumed values were identified in the data listings.

There were to be no assumed values for the standard sunscreen. If any subject had no erythema present, or all sites had erythema, then the results for that subject were not to be used.

According to the FDA guideline on testing procedures for sunscreens (2), the SPF value for the standard sunscreen, 8% homosalate, was to be within the range 4.47 ± 1.279 and the 95% CI for the mean SPF must contain the value 4.

The SPF for each of the 6 investigational materials was summarised (including 95% confidence intervals). Each individual subject’s SPF data were listed.

MED (TS) was summarised for each of the 6 investigational materials. MED (US) and repeat MED (US) were summarised for untreated skin.

MED (US), repeat MED (US) and MED (TS) details were listed for each subject along with immediate and 23 h (± 1 h) post irradiation assessments.

9.7.2.3 Analysis of Safety Variables

Throughout the study, all systemic adverse events, either observed by clinical staff or professional collaborators, or reported by the subject spontaneously or in response to a direct question, were evaluated by the investigator and noted in the adverse event section of the CRF. Observations of reactions (immediate or elevated responses, or
erythema) on designated skin sites were not deemed as adverse events. Any other responses required the Dermatologist to be contacted for confirmation, assessment and reporting.

Adverse events were reported by MedDRA system organ class and preferred term. All adverse events beginning before application of investigational products were excluded from the summary tables but were included in the data listings. The following tables were provided:

**Summary of adverse events**
- Number and percentage of subjects with at least one adverse event.
- Number and percentage of subjects with serious adverse events.
- Number and percentage of subjects with adverse events related to investigational product.
- Total number of adverse events.
- Total number of serious adverse events.
- Total number of adverse events related to investigational product.

Adverse events related to investigational product were defined as possibly related and probably related events.

Summaries of adverse events by severity and relationship to investigational product were also produced.

**9.7.3 Determination of Sample Size**
No formal sample size calculation was performed. The sample size was based on the recommendation given in the FDA guideline on testing procedures for sunscreens (2). Screening of a total number of 30 subjects was carried out in order to include a total number of 25 subjects in the main part of the study. From these 25 subjects valid data for analysis was to be obtained from at least 20 subjects.

**9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES**

**9.8.1 Changes in the Conduct of the Study**
It was planned in the protocol that the location of cutaneous adverse events should be recorded. Only cutaneous reactions that would not be captured in the assessment of immediate skin responses (Days 1 and 2) and in the erythema scores (Days 2 and 3) were to be recorded. By mistake, no specific space was given in the CRF for recording the location of such adverse events, and it was thus decided in agreement with the sponsor, that, if applicable, the location of the cutaneous adverse event should be stated in the field ‘Adverse Event (with additional comments)’ in the CRF. During the conduct of the clinical phase, however, no subjects experienced any cutaneous adverse events that could not be classified under the immediate skin responses or the erythema score.
After the database was locked, the database was reopened for correction of a data entry error discovered during the review process. This resulted in changes to TABLE 14.2.4 and Listing 16.2.5.6, and also resulted in changes to the text in Section 11.4.1. The error was discovered before finalising the report and the final report is thus based on the corrected database.

9.8.2 Changes in the Planned Analyses

It was planned in the protocol that MED (US), repeat MED (US) and MED (TS) summary statistics would include 95% confidence intervals. However, 95% confidence intervals were not included for these summary statistics as it was considered not to be relevant.

It was not planned in the protocol that immediate skin response and post irradiation (erythema) data for untreated skin and treated skin would be summarised. However, summary tables were provided for these data to enable any cutaneous reactions (which would not be recorded as adverse events) to be identified.

Immediate skin responses were summarised by count of the first observation of any reaction to irradiation, at the length of UV exposure at which the reaction was first observed. The lengths of UV exposure are identified in the summary tables as 1 to 8, with 1 being the shortest UV exposure and 8 being the longest. Any subject without a reaction at any length of UV exposure was counted as having 'no response'.

Erythema (post-irradiation assessment) scores were summarised by the highest erythema score.
10 RESULTS

10.1 DISPOSITION OF SUBJECTS
A total of 31 subjects was screened for this study. Of this number, 6 subjects did not meet the inclusion/exclusion criteria. The number of subjects entering, withdrawing and completing the study is summarised in TABLE 14.1.1 and individual subject details are presented in Data Listing 16.2.1.

Twenty-five (25) subjects entered the study and received the first UV exposure on Day 1. All 25 subjects returned to the test facility on Day 2 for erythema scoring. A MED (US) could not be established for 2 subjects (Subjects  and  and so they were withdrawn. Twenty-three (23) subjects completed the study.

The number of subjects screened, rejected and entered into this study are presented in Section 10.1.1.
10.1.1 Flow Chart of Disposition of Subjects

![Flow Chart Diagram]

* Subjects [●] and [●] had scores of 0 (no visible reaction) after all 8 UV exposures to untreated skin and so no MED(US) could be calculated.

** Subject [●] had scores of 0 (no visible reaction) after all 8 UV exposures to untreated skin and therefore a repeat MED(US) could not be calculated.
10.2 PROTOCOL DEVIATIONS
There were no protocol deviations recorded, as indicated in Data Listing 16.2.2, and no subjects failed the inclusion/exclusion criteria, as indicated in Data Listing 16.2.3.
11 BASELINE AND UV EXPOSURE EVALUATION

11.1 DATASETS ANALYSED
Subject disposition is given in TABLE 14.1. All subjects who received the first UV exposure on Day 1 were included in the ‘All Subjects’ dataset. This dataset was used for summaries of demographic details and the assessments of untreated skin. A MED (US) could not be established for 2 subjects and so they were withdrawn before application of any of the investigational materials. Twenty-three (23) subjects had the 6 investigational materials applied and received the second UV exposure on Day 2. These 23 subjects comprised the safety dataset.

11.2 DEMOGRAPHIC AND BASELINE FEATURES

11.2.1 Demographics
Demographic details recorded at screening are summarised in TABLE 14.1.2 and individual demographic details are listed in Data Listing 16.2.4.1.

The mean (SD) age of enrolled subjects was 34.5 (11.7) years. Eleven subjects (44.0%) were male and 14 subjects (56.0%) were female. All 25 subjects who entered the study were white.

11.2.2 Medical History
Details of the medical, surgical and dermatological histories obtained at screening are recorded in Data Listings 16.2.4.2.1 to 16.2.4.2.4. Details of any pregnancy tests performed at screening are recorded in Data Listing 16.2.4.2.5.

None of the subjects had a medical, surgical or dermatological history which precluded his or her enrolment in the study. Subject had moles present on her back, but these were not present at the test sites.

Eight subjects had a pregnancy test performed at screening. All 8 test results were negative.

11.2.3 Concomitant Medications
Details of medications taken at screening are presented in Data Listing 16.2.4.3.1. Six subjects were taking medication at screening that was ongoing during the study. Subject was taking hormone replacement therapy, thyroxine for an underactive thyroid, and sumatriptan (as required) for migraine. Subjects and were taking hormone replacement therapy. Subjects and were taking oral contraceptives and Subject was taking progestogens as a 3 monthly intramuscular injection for contraception. None of the ongoing medications precluded any subject from enrolment in the study.
No subject required other concomitant medication during the course of the study, as detailed in Data Listing 16.2.4.3.2.

11.3 RESULTS OF TREATMENT COMPLIANCE MEASUREMENT

Admission details are presented in Data Listing 16.2.4.5. Individual details of duration of irradiation are presented in Data Listings 16.2.5.1 and 16.2.5.2. Individual details of application of investigational materials to test sites are presented in Data Listing 16.2.5.4. All subjects received an application of each of the investigational materials in accordance with the protocol and amendments, except for 2 subjects. A MED (US) could not be established for Subjects and and so they were withdrawn before application of any of the investigational materials.

11.4 UV EXPOSURE RESULTS

11.4.1 Erythema

Post irradiation assessments of erythema are summarised in TABLE 14.2.7 for untreated skin and in TABLE 14.2.6 for treated skin. Individual 23 h (± 1 h) post irradiation assessments of erythema are given in Data Listing 16.2.5.3 for the Day 1 irradiation of untreated skin and in Data Listing 16.2.5.6 for the Day 2 irradiation of untreated and treated skin.

After the Day 1 irradiation of untreated skin, the highest erythema score at 23 h (± 1 h) was 2 (distinct unambiguous erythema over the entire irradiation site with clearly defined borders), recorded for 5 subjects (20.0%). Subjects and had a score of 2 at the 2 longest UV exposures (2.4 and 3.0 min of exposure) and Subject had a score of 2 at the 3 longest UV exposures (1.9, 2.4 and 3.0 min of exposure). Two subjects (8.0%, Subjects and had scores of 0 (no visible reaction) after all 8 UV exposures and so were withdrawn from the study. The remaining 18 subjects (72.0%) had scores of 1 (slight but unambiguous erythema over the entire irradiation site with clearly defined borders) after one or more of the UV exposures.

After the Day 2 irradiation of untreated skin, the highest erythema score at 23 h (± 1 h) was 1, recorded for 22 out of 23 subjects (95.7%). One subject (Subject had a maximum erythema score of 0, and hence a repeat MED (US) could not be calculated for this subject.

After the Day 2 irradiation of treated skin, the highest erythema score at 23 h (± 1 h) was 1, recorded for 23 out of 23 subjects (100%) for Daivobet/Dovobet ointment, for 22 out of 23 subjects (95.7%) for Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, standard emollient (Diprobase Cream) and for standard sunscreen (8% homosalate).
Two subjects had a maximum erythema score of 0 after all 8 UV exposures for one or more of the investigational materials: Subject [A] for standard sunscreen and standard emollient and and Subject [B] for Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution and Daivonex/Dovonex scalp solution vehicle. These 2 subjects had erythema scores of 1 after at least one of the 8 UV exposures for the remaining investigational materials.

11.4.2 MED (US), Repeat MED (US) and MED (TS)

MED (US), repeat MED (US) and MED (TS) are summarised in TABLE 14.2.2 and TABLE 14.2.1, respectively and individual data are presented in Data Listing 16.2.5.3 for MED (US) and Data Listings 16.2.5.6 and 16.2.5.7 for repeat MED (US) and MED (TS).

A MED (US) was calculated for 23 subjects from erythema scores at 23 h (± 1 h) after the Day 1 irradiation. Two subjects (Subjects [A] and [B]) had scores of 0 (no visible reaction) after all 8 UV exposures and so no MED (US) could be calculated. A repeat MED (US) was calculated for 22 subjects from erythema scores at 23 h (± 1 h) after the Day 2 irradiation. Subject [C] had scores of 0 after all 8 UV exposures to untreated skin and therefore a repeat MED (US) could not be calculated.

11.4.2.1 Mean (SD) MED (US), repeat MED (US) and MED (TS)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean (min)</th>
<th>SD (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED (US)</td>
<td>23</td>
<td>1.66</td>
<td>0.55</td>
</tr>
<tr>
<td>Repeat MED (US)</td>
<td>22</td>
<td>2.30</td>
<td>0.81</td>
</tr>
<tr>
<td>Daivobet/Dovobet ointment</td>
<td>23</td>
<td>2.45</td>
<td>0.88</td>
</tr>
<tr>
<td>Daivobet/Dovobet ointment vehicle</td>
<td>23</td>
<td>2.58</td>
<td>1.05</td>
</tr>
<tr>
<td>Daivonex/Dovonex scalp solution</td>
<td>23</td>
<td>2.16</td>
<td>1.00</td>
</tr>
<tr>
<td>Daivonex/Dovonex scalp solution vehicle</td>
<td>23</td>
<td>2.19</td>
<td>1.00</td>
</tr>
<tr>
<td>Standard emollient, Diprobase Cream</td>
<td>23</td>
<td>2.27</td>
<td>0.84</td>
</tr>
<tr>
<td>Standard sunscreen 8% homosalate</td>
<td>22*</td>
<td>6.74</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Note: Data presented above are summarised in TABLE 14.2.1 and TABLE 14.2.2.

*Subject [D] had a maximum erythema score of 0 with standard sunscreen so no MED (TS) could be calculated.

Mean MED (TS) for Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, and standard emollient, Diprobase Cream were broadly similar (2.16 min to 2.58 min) and all were similar to mean repeat MED (US) results (2.30 min).

11.4.3 SPF

Mean SPF for all 6 investigational materials is summarised in TABLE 14.2.3 and individual subject SPF data are presented in Data Listing 16.2.5.7. Subject [E] did not have SPFs calculated for any of the 6 investigational materials as untreated skin erythema scores
were 0 after all 8 UV exposures for this subject, therefore a repeat MED (US) could not be calculated. Subject had an erythema score of 0 after all 8 UV exposures for the standard sunscreen, therefore no MED (TS) could be determined for the sunscreen and SPFs were not calculated for the 6 investigational materials.

### 11.4.3.1 Mean (CI) SPF results

<table>
<thead>
<tr>
<th>Material</th>
<th>N</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daivobet/Dovobet ointment</td>
<td>21</td>
<td>1.11</td>
<td>0.96 - 1.27</td>
</tr>
<tr>
<td>Daivobet/Dovobet ointment vehicle</td>
<td>21</td>
<td>1.18</td>
<td>1.00 - 1.35</td>
</tr>
<tr>
<td>Daivonex/Dovonex scalp solution</td>
<td>21</td>
<td>0.98</td>
<td>0.84 - 1.13</td>
</tr>
<tr>
<td>Daivonex/Dovonex scalp solution vehicle</td>
<td>21</td>
<td>1.00</td>
<td>0.83 - 1.16</td>
</tr>
<tr>
<td>Standard emollient (Diprobase Cream)</td>
<td>21</td>
<td>1.01</td>
<td>0.88 - 1.15</td>
</tr>
<tr>
<td>Standard sunscreen (8% homosalate)</td>
<td>21</td>
<td>3.06</td>
<td>2.58 - 3.54</td>
</tr>
</tbody>
</table>

Note: Data presented above are summarised in TABLE 14.2.3.

Mean SPF results for Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, and standard emollient, Diprobase 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).

Mean (CI) SPF results for the standard sunscreen 8% homosalate were 3.06 (2.58 to 3.54). The mean SPF was lower than the expected range as stated in the protocol and Section 9.7.2.2.1 (see filenote and technical document, Appendix XIII).

### 11.4.4 Immediate Responses

Immediate skin responses to UV exposure are summarised in TABLE 14.2.5 for untreated skin and in TABLE 14.2.4 for treated skin. Individual subject immediate skin responses are presented in Data Listing 16.2.5.2 for untreated skin and in Data Listing 16.2.5.5 for treated skin.

On Day 1, 6 out of 25 subjects (24.0%) had no immediate responses to UV exposure of untreated skin, and on Day 2, 6 out of 23 subjects (26.1%) had no immediate responses to UV exposure of untreated skin. No subject had oedema or a spreading reaction outside the irradiation site. Darkening and redness were recorded after both Day 1 and Day 2 irradiation of untreated skin, with some evidence of more reddening at the longer UV exposures.

No immediate skin responses were recorded for 16 out of 23 subjects (69.6%) after UV exposure to the Daivobet/Dovobet ointment and Daivonex/Dovonex scalp solution test sites, for 19 out of 23 subjects (82.6%) after UV exposure to the Daivobet/Dovobet ointment vehicle test site, for 15 out of 23 subjects (65.2%) after UV exposure to the Daivonex/Dovonex scalp solution vehicle test site, for 21 out of 23...
subjects (91.3%) after UV exposure to the standard emollient test site, and for 11 out of 23 subjects (47.8%) after UV exposure to the standard sunscreen test site.

The most commonly recorded response was immediate pigment darkening, recorded for at least one subject at one or more UV exposure length for all of the investigational materials, except the standard emollient for which no immediate pigment darkening was recorded. There was some evidence of an increase in recorded darkening with longer UV exposures, and the numbers of subjects recording darkening were broadly similar for all the investigational materials, except the standard emollient.

No subject had oedema or a spreading reaction outside the irradiation site. Reddening was recorded for one subject (Subject [■]) after UV exposure to the standard sunscreen test site. Subjects [■] and [■] had a marked reaction to the adhesive tape used to delineate the test sites (Subject [■] standard emollient and standard sunscreen test sites, and Subject [■] standard emollient test site).

11.5 UV EXPOSURE CONCLUSIONS

Mean SPF results for Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle, and standard emollient, Diprobase 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 for the standard sunscreen 8% homosalate was lower than the expected range as stated in the protocol. The 8% homosalate standard sunscreen did demonstrate protection to UV.

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.
12 SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Individual subject details of irradiation of untreated skin are presented in Data Listings 16.2.5.1 and 16.2.5.2. Individual subject details of irradiation of treated skin are presented in Data Listings 16.2.5.4 and 16.2.5.5.

On Day 1, 25 subjects received 8 UV exposures to an area of untreated skin in an ascending geometric series from 0.6 min to 3.0 min. A MED (US) could not be determined for 2 subjects (Subjects and and they were withdrawn from the study. The remaining 23 subjects received a single application of 0.1 g of each of 6 investigational materials followed by 8 UV exposures to each of the 6 test material test sites. The length of the UV exposures to these sites was a geometric series derived from the first MED (US). All 23 subjects also received a further 8 UV exposures to a second area of untreated skin to enable calculation of a repeat MED (US).

12.2 ADVERSE EVENTS

Adverse events are summarised in TABLE 14.3.1 to TABLE 14.3.3 and are presented for individual subjects in Data Listings 16.2.7.1 to 16.2.7.3.

Pre-application adverse events were recorded for 2 subjects. Subject had nasopharyngitis on Day 1 of the study, before application of the investigational materials. The event was not treated and was ongoing at the end of the study. Subject had pharyngolaryngeal pain and ear pain on Day 1 of the study, before application of the investigational materials. The events were not treated and were ongoing at the end of the study. No pre-application adverse event was considered by the clinical investigator to interfere with the aims of the study.

There were no adverse events recorded after application of investigational materials and no serious adverse events recorded for any subject during the study. No subject was withdrawn from the study because of an adverse event.

12.3 LOCAL REACTIONS

The incidence of immediate skin responses and erythema is discussed in Sections 11.4.4 and 11.4.1, respectively.

12.4 SAFETY CONCLUSIONS

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

13.1 DISCUSSION

13.1.1 Summary of Results
In this within subject comparison study, the mean SPF results for Daivobet/Dovobet ointment, Daivobet/Dovobet ointment vehicle, Daivonex/Dovonex scalp solution, Daivonex/Dovonex scalp solution vehicle and a standard emollient, Diprobase 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). The mean SPF of the standard sunscreen (8% homosalate) was 3.06 (95% CI 2.58 to 3.54).

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. No adverse events were recorded for any subject after application of any of the 6 investigational materials.

13.1.2 Design and Conduct of the Study
It was planned that 20 subjects should complete the study. No formal sample size calculation was performed but the sample size was based on the Testing Procedures given in the FDA Guideline For Sunscreen Products For Over-The-Counter Human Use (2). A total of 25 subjects entered the study and 23 completed the study. The number of subjects included in the analysis was therefore in accordance with the FDA Guideline for this type of study. Product application procedures were standardised with the use of a Standard Operating Procedure (SOP) and the technicians were fully trained in this procedure. The subjects included in the study consisted of 11 male and 14 female Caucasian subjects, mean age 34.5 ± 11.7 years. All subjects met the inclusion and exclusion criteria and no protocol deviations or GCP compliance issues were recorded during the study. Randomisation procedures were followed and the study blind was maintained as planned.

While the FDA Guideline for SPF determination concerns investigations of sunscreen-containing materials, the investigational materials in the present study did not contain sunscreens. However, in the absence of an ‘evaluation of UV penetration model’, this guideline was considered suitable. A within-subject comparison was considered the most appropriate study design by the clinical investigator to assess the UV penetration with different investigational materials. The study design was based on the FDA Guideline.
13.1.3 Interpretation of Study Results

The aim of the study was to evaluate whether the application of investigational materials with or without active ingredients would induce further UV penetration in comparison with untreated skin.

The evaluation of erythemal response was conducted for the investigational materials and compared with the erythemal response observed without treatment. In all cases, the 95% CI of the SPF for the investigational materials contained the value 1. The erythemal responses to the investigational materials were broadly similar (95% CI contained the value 1) to that observed for untreated skin. It can be concluded that application of investigational materials did not induce further UV penetration in comparison with untreated skin. The primary objective of the study had a satisfactory conclusion.

The result obtained for the standard sunscreen was marginally lower than expected. The standard sunscreen was included to show that the method could show protection. Analysis of the standard sunscreen was conducted by [redacted] according to the method of analysis given in the FDA guideline (2) and found to contain the active ingredient homosalate, but in a concentration deviating from 8%. It had been refrigerated from the time of manufacture (July 2003) as required according to the specified storage conditions. This standard sunscreen is known to be unstable which may explain the deviation in the concentration of homosalate. The result did demonstrate an SPF, albeit slightly lower than expected. This was, however, considered not to affect the integrity of the results. Another standard was included in the test, a standard emollient without any sun protection. The 95% CI results for this standard marketed emollient also contained the value 1 and as such supported the validity of the results.

Inherently, the method may also be prone to some uncertainty including the method of application and distribution of substances, and the assessment of erythema. If the lower SPF value for the standard sunscreen (homosalate) can be explained by the application of a smaller amount of standard sunscreen than stated in the FDA Guideline, the sun-protection factors for the test substances could actually be higher than estimated. If the low SPF value for the standard sunscreen indicated a general problem with the method, then the SPF value for the test substances could be too low as well, which would mean that the sun protection factor may actually be higher than estimated.

There was some evidence of an increase in immediate skin responses (immediate pigment darkening) with longer UV exposures for all investigational materials, except for the standard emollient.

The safety data showed no post-application adverse events and there were no adverse drug reactions to the investigational materials and subsequent UV exposure.
13.2 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. 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.
14 SUMMARY TABLES AND FIGURES

14.1 DEMOGRAPHIC DATA
### TABLE 14.1.1

Subject Disposition  
Summary Statistics: All Subjects

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Number of Subjects Entering Study</td>
<td>25</td>
</tr>
<tr>
<td>Number and (%) of Subjects Withdrawn</td>
<td>2 (8.0%)</td>
</tr>
<tr>
<td>Number and (%) of Subjects in Safety Dataset</td>
<td>23 (92.0%)</td>
</tr>
<tr>
<td>Number and (%) of Subjects Who Completed Trial</td>
<td>23 (92.0%)</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.1  
Safety dataset contains all subjects receiving application of test material
TABLE 14.1.2
Demographic Details at Screening
Summary Statistics: All Subjects

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Mean</td>
<td>34.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>35.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>MALE N (%)</td>
<td>11 (44.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FEMALE N (%)</td>
<td>14 (56.0%)</td>
<td></td>
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<tr>
<td>Race</td>
<td>WHITE N (%)</td>
<td>25 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.4.1.
14.2 UV EXPOSURE DATA
### TABLE 14.2.1

<table>
<thead>
<tr>
<th>Test Material</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIVOSET/DOVOBET OINTMENT</td>
<td>23</td>
<td>2.45</td>
<td>0.88</td>
<td>2.40</td>
<td>1.0</td>
<td>4.7</td>
</tr>
<tr>
<td>DAIVOSET/DOVOBET OINTMENT VEHICLE</td>
<td>23</td>
<td>2.58</td>
<td>1.05</td>
<td>2.40</td>
<td>1.3</td>
<td>5.9</td>
</tr>
<tr>
<td>DAIVONEX/DOVONEX SCALP SOLUTION</td>
<td>23</td>
<td>2.16</td>
<td>1.00</td>
<td>1.90</td>
<td>1.0</td>
<td>5.9</td>
</tr>
<tr>
<td>DAIVONEX/DOVONEX SCALP SOLUTION VEHICLE</td>
<td>23</td>
<td>2.19</td>
<td>1.00</td>
<td>1.90</td>
<td>1.0</td>
<td>5.9</td>
</tr>
<tr>
<td>EMOLLIENT (DIPROBASE CREAM)</td>
<td>23</td>
<td>2.27</td>
<td>0.84</td>
<td>2.30</td>
<td>1.0</td>
<td>4.7</td>
</tr>
<tr>
<td>STANDARD SUNSCREEN (8% HOMOSALATE)</td>
<td>22</td>
<td>6.74</td>
<td>2.52</td>
<td>6.10</td>
<td>3.2</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listings 16.2.5.6 and 16.2.5.7
If MED (TS) recorded as >n mins for sunscreen - data not used in summary stats
If MED (TS) recorded as >n mins for other treatments then n*1.25 used in summary stats

03MAY2004 10:47
TABLE 14.2.2

Minimal Erythema Dose (MED) (mins)
Untreated Skin
Summary Statistics: All Subjects

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>MED (US)</td>
<td>23</td>
<td>1.66</td>
<td>0.55</td>
<td>1.50</td>
<td>0.8</td>
<td>3.0</td>
</tr>
<tr>
<td>REPEAT MED (US)</td>
<td>22</td>
<td>2.30</td>
<td>0.81</td>
<td>2.15</td>
<td>1.2</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listings 16.2.5.3, 16.2.5.6 and 16.2.5.7. If MED (US) recorded as >n mins - data not used in summary stats.
**TABLE 14.2.3**

Sun Protection Factor
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Test Material</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
<th>95% Upper CI</th>
<th>95% Lower CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIVOBET/DOVOBET OINTMENT</td>
<td>21</td>
<td>1.11</td>
<td>0.34</td>
<td>1.1</td>
<td>0.6</td>
<td>1.6</td>
<td>1.27</td>
<td>0.96</td>
</tr>
<tr>
<td>DAIVOBET/DOVOBET OINTMENT VEHICLE</td>
<td>21</td>
<td>1.18</td>
<td>0.38</td>
<td>1.1</td>
<td>0.6</td>
<td>1.9</td>
<td>1.35</td>
<td>1.00</td>
</tr>
<tr>
<td>DAIVONEX/DOVONEX SCALP SOLUTION</td>
<td>21</td>
<td>0.98</td>
<td>0.32</td>
<td>0.9</td>
<td>0.5</td>
<td>1.6</td>
<td>1.13</td>
<td>0.84</td>
</tr>
<tr>
<td>DAIVONEX/DOVONEX SCALP SOLUTION VEHICLE</td>
<td>21</td>
<td>1.00</td>
<td>0.36</td>
<td>1.0</td>
<td>0.5</td>
<td>1.9</td>
<td>1.16</td>
<td>0.83</td>
</tr>
<tr>
<td>EMOLLIENT (DIPROBASE CREAM)</td>
<td>21</td>
<td>1.01</td>
<td>0.30</td>
<td>1.0</td>
<td>0.5</td>
<td>1.6</td>
<td>1.15</td>
<td>0.88</td>
</tr>
<tr>
<td>STANDARD SUNSCREEN (8% HOMOSALATE)</td>
<td>21</td>
<td>3.06</td>
<td>1.05</td>
<td>3.2</td>
<td>1.1</td>
<td>6.3</td>
<td>3.54</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.7

Subject ✘: No SPF obtained for standard sunscreen - therefore no SPF recorded

Subject ✗: Repeat MED (US) >3.0 - therefore no SPF calculated
TABLE 14.2.4
Immediate Response
Treated Skin
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Response (N=23)</th>
<th>Sub-site</th>
<th>D/DO (%)</th>
<th>D/DOV (%)</th>
<th>D/DSS (%)</th>
<th>D/DSSV (%)</th>
<th>E (%)</th>
<th>SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO RESPONSE</td>
<td></td>
<td>16 (69.6%)</td>
<td>19 (82.6%)</td>
<td>16 (69.6%)</td>
<td>15 (65.2%)</td>
<td>21 (91.3%)</td>
<td>11 (47.8%)</td>
</tr>
<tr>
<td>REACTION</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>1 (4.3%)</td>
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</tr>
<tr>
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<td>2</td>
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<tr>
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<td>0</td>
</tr>
<tr>
<td></td>
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</table>

Note: The data in this table are presented in listing 16.2.5.5
Response shown at first exposure it occurred (also occurred at all higher exposures)
Key: D/DO=davobet/dovobet ointment D/DOV=davobet/dovobet ointment vehicle
D/DSS=davonex/dovonex scalp solution D/DSSV=davonex/dovonex scalp solution vehicle
E=standard emollient (diprobase cream) SS=standard sunscreen (8% homosalate)
Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template - Darkening=Immediate pigment darkening - Reddening=Immediate reddening
Reaction o/s=Spreading reaction outwith the irradiation site

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**TABLE 14.2.4**

Immediate Response
Treated Skin
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Sub-site (N=23)</th>
<th>D/DDO (%)</th>
<th>D/DDOV (%)</th>
<th>D/DSS (%)</th>
<th>D/DSSV (%)</th>
<th>E (%)</th>
<th>SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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</tbody>
</table>

**Note:** The data in this table are presented in listing 16.2.5.5

- Response shown at first exposure it occurred (also occurred at all higher exposures)
- Key:
  - D/DDO = daivobet / dovobet ointment
  - D/DDOV = daivobet / dovobet ointment vehicle
  - D/DSS = daivonex / dovonex scalp solution
  - D/DSSV = daivonex / dovonex scalp solution vehicle
  - E = standard emollient (diprobase cream)
  - SS = standard sunscreen (8% homosalate)
  - Reaction = Marked reaction to adhesive tape used to delineate the test site and secure the template
  - Darkening = Immediate pigment darkening
  - Reddening = Immediate reddening
  - Reaction o/s = Spreading reaction outwith the irradiation site

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### TABLE 14.2.4

Immediate Response  
Treated Skin  
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>D/DO (%)</th>
<th>D/DOV (%)</th>
<th>D/DSS (%)</th>
<th>D/DSSV (%)</th>
<th>E (%)</th>
<th>SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARKENING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (8.7%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>0</td>
<td>1 (4.3%)</td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>1 (4.3%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td></td>
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<td>1 (4.3%)</td>
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<td>2 (8.7%)</td>
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<td>3 (13.0%)</td>
<td></td>
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<tr>
<td>6</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
<td>2 (8.7%)</td>
<td>0</td>
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<td>3 (13.0%)</td>
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<tr>
<td>7</td>
<td>3 (13.0%)</td>
<td>0</td>
<td>2 (8.7%)</td>
<td>3 (13.0%)</td>
<td>0</td>
<td>1 (4.3%)</td>
<td></td>
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<tr>
<td>8</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
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<td>2 (8.7%)</td>
<td>0</td>
<td>1 (4.3%)</td>
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</table>

Note: The data in this table are presented in listing 16.2.5.5

Response shown at first exposure if occurred (also occurred at all higher exposures)

Key:
- D/DO: daivobet/dovobet ointment
- D/DOV: daivobet/dovobet ointment vehicle
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- SS: standard sunscreen (8% homosalate)

Reaction:
- Marked reaction to adhesive tape used to delineate the test site and secure the template - Darkening: Immediate pigment darkening - Reddening: Immediate reddening
- Reaction o/s: Spreading reaction outwith the irradiation site

03MAY2004 10:50
TABLE 14.2.4

Immediate Response
Treated Skin
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Response (N=23)</th>
<th>Sub-site</th>
<th>D/DO (n (%))</th>
<th>D/DOV (n (%))</th>
<th>D/DSS (n (%))</th>
<th>D/DSSV (n (%))</th>
<th>E (n (%))</th>
<th>SS (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDDENING</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.5
Response shown at first exposure it occurred (also occurred at all higher exposures)
Key: D/DO=daivobet/dovobet ointment D/DOV=daivobet/dovobet ointment vehicle
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Reaction o/s=Spreading reaction outwith the irradiation site

03MAY2004 10:50
TABLE 14.2.4
Immediate Response
Treated Skin
Summary Statistics: Safety Dataset

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>D/DO (%)</th>
<th>D/DOV (%)</th>
<th>D/DSS (%)</th>
<th>D/DSSV (%)</th>
<th>E (%)</th>
<th>SS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACTION O/S</td>
<td>1</td>
<td>0</td>
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</tr>
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</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.5
Response shown at first exposure it occurred (also occurred at all higher exposures)
Key: D/DO=daivobet/dovobet ointment D/DOV=daivobet/dovobet ointment vehicle
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Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
Darkening=Immediate pigment darkening
Reddening=Immediate reddening
Reaction o/s=Spreading reaction outwith the irradiation site

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### TABLE 14.2.5

**Immediate Response**
**Untreated Skin**
**Summary Statistics: All Subjects**

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>MED (US) (N=25) n (%)</th>
<th>REPEAT MED (US) (N=23) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO RESPONSE</td>
<td></td>
<td>6 (24.0%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>REACTION</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td></td>
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<tr>
<td>8</td>
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</table>

Note: The data in this table are presented in listing 16.2.5.2.

Response shown at first exposure it occurred (also occurred at all higher exposures)

Key: Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
Darkening=Immediate pigment darkening - Reddening=Immediate reddening
Reaction o/s=Spreading reaction outwith the irradiation site

03MAY2004 10:51
### TABLE 14.2.5

Immediate Response
Untreated Skin
Summary Statistics: All Subjects

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>MED (US) (N=25)</th>
<th>REPEAT MED (US) (N=23)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
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<td></td>
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</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.2

Response shown at first exposure it occurred (also occurred at all higher exposures)

Key: Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
Darkening=Immediate pigment darkening - Reddening=Immediate reddening
Reaction o/s=Spreading reaction outwith the irradiation site
### TABLE 14.2.5

**Immediate Response**

**Untreated Skin**

**Summary Statistics: All Subjects**

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>MED (US) (N=25)</th>
<th>Repeat MED (US) (N=23)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
<td>n</td>
</tr>
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<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1 (4.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0 (0%)</td>
<td>2 (8.7%)</td>
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<td>4</td>
<td>2 (8.0%)</td>
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<td></td>
<td>5</td>
<td>3 (12.0%)</td>
<td>4 (17.4%)</td>
</tr>
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<td></td>
<td>6</td>
<td>2 (8.0%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
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<td>7</td>
<td>4 (16.0%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.2

Response shown at first exposure it occurred (also occurred at all higher exposures)

Key:
- Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
- Darkening=Immediate pigment darkening - Reddening=Immediate reddening
- Reaction o/s=Spreading reaction out with the irradiation site

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### TABLE 14.2.5

**Immediate Response**

**Untreated Skin**

**Summary Statistics: All Subjects**

<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>MED (US) (N=25)</th>
<th>REFBEAT MED (US) (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>REDDENING</td>
<td>1 0</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 0</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 0</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 0</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 0</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 3 (12.0%)</td>
<td>2 (8.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 4 (16.0%)</td>
<td>3 (13.0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 0</td>
<td>3 (13.0%)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The data in this table are presented in listing 16.2.5.2.

**Response shown at first exposure it occurred (also occurred at all higher exposures)**

**Key:**
- Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
- Darkening=Immediate pigment darkening - Reddening=Immediate reddening
- Reaction o/s=Spreading reaction outwith the irradiation site
<table>
<thead>
<tr>
<th>Response</th>
<th>Sub-site</th>
<th>MED (US)</th>
<th>Repeat MED (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N=25)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>REACTION O/S</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.2
Response shown at first exposure it occurred (also occurred at all higher exposures)
Key: Reaction=Marked reaction to adhesive tape used to delineate the test site and secure the template
Darkening=Immediate pigment darkening - Reddening=Immediate reddening
Reaction o/s=Spreading reaction outwith the irradiation site
<table>
<thead>
<tr>
<th>Erythema Level</th>
<th>D/DO</th>
<th>D/DOV</th>
<th>D/DSS</th>
<th>D/DSSV</th>
<th>E</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=23)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>1</td>
<td>23 (100.0%)</td>
<td>22 (95.7%)</td>
<td>22 (95.7%)</td>
<td>22 (95.7%)</td>
<td>22 (95.7%)</td>
<td>22 (95.7%)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.5.6.

Key:
- D/DO = daivobet/dovobet ointment
- D/DOV = daivobet/dovobet ointment vehicle
- D/DSS = daivonex/dovonex scalp solution
- D/DSSV = daivonex/dovonex scalp solution vehicle
- E = standard emollient (diprobase cream)
- SS = standard sunscreen (8% homosalate)
- 0 = No visible reaction
- 1 = Slight but unambiguous erythema over the entire irradiation site with clearly defined borders
- 2 = Distinct unambiguous erythema over the entire irradiation site with clearly defined borders
- 3 = Intense erythema
- 4 = Visible non-erythematous reaction (tanning)
### TABLE 14.2.7

**Post Irradiation Assessment**

**Untreated Skin**

**Summary Statistics: All Subjects**

<table>
<thead>
<tr>
<th>Maximum Erythema</th>
<th>MED (US) (N=25)</th>
<th>REPEAT MED (US) (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n ( % )</td>
<td>n ( % )</td>
</tr>
<tr>
<td>0</td>
<td>2 ( 8.0% )</td>
<td>1 ( 4.3% )</td>
</tr>
<tr>
<td>1</td>
<td>18 ( 72.0% )</td>
<td>22 ( 95.7% )</td>
</tr>
<tr>
<td>2</td>
<td>5 ( 20.0% )</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note: The data in this table are presented in listings 16.2.5.3 and 16.2.5.6*

**Key:**
- 0 = No visible reaction
- 1 = Slight but unambiguous erythema over the entire irradiation site with clearly defined borders (MED)
- 2 = Distinct unambiguous erythema over the entire irradiation site with clearly defined borders
- 3 = Intense erythema
- 4 = Visible non-erythemal reaction (tanning)
14.3 ADVERSE EVENTS
### TABLE 14.3.1

Adverse Events After Application of Investigational Product
Summary Statistics: All Subjects

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects to whom Investigational Product Applied</td>
<td>23</td>
</tr>
<tr>
<td>Number and (%) of Subjects with Adverse Events</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Number and (%) of Subjects with Adverse Events Related to Investigational Product #</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Number and (%) of Subjects with Serious Adverse Events</td>
<td>0 (0.0 %)</td>
</tr>
<tr>
<td>Number of Adverse Events</td>
<td>0</td>
</tr>
<tr>
<td>Number of Adverse Events Related to Investigational Product #</td>
<td>0</td>
</tr>
<tr>
<td>Number of Serious Adverse Events</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: The data in this table are presented in listing 16.2.7.3

Subjects and withdrew after Day 1 as no definite value obtained for MED (US)

# Adverse events related to investigational product are defined as those with a relationship of possible or probable
### Table 14.3.2

Adverse Events After Application of Investigational Product
By MedDRA System Organ Class and Preferred Term
All Reported Events by Severity
Summary Statistics: All Subjects

**NO POST-APPLICATION ADVERSE EVENTS WERE RECORDED**
Table 14.3.3

Adverse Events After Application of Investigational Product
By MedDRA System Organ Class and Preferred Term
All Reported Events by Relationship
Summary Statistics: All Subjects

No Post-Application Adverse Events Were Recorded
15 REFERENCES


16 LIST OF APPENDICES

Appendix I  Protocol and Protocol Amendment
Appendix II  Sample Case Report Form
Appendix III  List of Ethics Committee Approvals
Appendix IV  List of Investigators and Other Significant Study Personnel
Appendix V  Declaration of the Clinical Investigator
Appendix VI  Batch Numbers of Material Used
Appendix VII  Randomisation Schemes and Codes
Appendix VIII  Quality Assurance Statement
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Appendix XI  Publications Based on the Study
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Appendix XV  Data Listings – Protocol Deviations
Appendix XVI  Data Listings – Inclusion/Exclusion Criteria
Appendix XVII  Data Listings – Demographic Data
Appendix XVIII  Data Listings – UV Exposure Data
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