Clinical Study Report

HUMAN SKIN BLANCHING ASSAY

IN VIVO BIOEQUIVALENCE STUDY OF BETAMETHASONE DIPROPIONATE IN DAIVOBET/DOVOBET GEL AND DIPROSONE OINTMENT ACCORDING TO FDA GUIDELINE FOR VASOCONSTRICTOR BIOASSAY

Part I – Pilot Study with the reference ointment
Part II – Pivotal Study

A Phase I, single centre, randomised, Investigator blinded study with intra-individual comparison of treatments

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.
1 CLINICAL STUDY REPORT APPROVAL

1.1 APPROVAL STATEMENT
On behalf of LEO, only the Medical Director, Medical Department, LEO DK, the Head of Biostatistics Department, and the Director, International Clinical Development, LEO, are authorised to approve the Clinical Study Report.

The following persons have approved this Clinical Study Report using electronic signatures as presented on the last page of this document.

[Signature]
LEO DK

[Signature]
Biostatistics Department

[Signature]
International Clinical Development

1.2 APPROVAL STATEMENT, INVESTIGATORS
On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report.

The International Co-ordinating Investigator

[Signature]
MD

has approved this report as presented on the International Co-ordinating Investigator Clinical Study Report Approval Form adjoined as a separate page to this document.
2 REPORT STATEMENTS

2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE
This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports; E6 Good Clinical Practice; and E9 Statistical Principles for Clinical Trials).

2.2 TRADEMARKS
DAIVO BET/DOVOBET is a trademark owned and in use by LEO Pharma A/S (or its subsidiaries).

DIPROSONE is a trademark owned and in use by Schering-Plough Corporation (or its subsidiaries).
2.3 STUDY AUTHENTICATION

**AUTHENTICATION FORM**

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**Protocol Code Number:** MBL 0403 FR

**Report Date (DD-MM-YYYY):** 20-MAR-2007

**TF Index No.:** 16.9167

**Report Title:** In vivo bioequivalence study of betamethasone dipropionate in DAIVOBET/DOVOBET gel and DIPROSONE ointment according to FDA Guideline for vasoconstrictor bioassay

This study was performed in compliance with the Good Clinical Practice (GCP) standard issued by the International Conference on Harmonisation (ICH), the Declaration of Helsinki with subsequent amendments, and respecting national rules/regulations.

The study was performed in accordance with the approved Study Protocol and with LEO Pharma Standard Operating Procedures for GCP. The report provides a true and accurate record of the results obtained.

**Authorised by:** PCPC

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**Distribution:** Original → Trial Master File (as part of Final Study Report)

**Version:** 01-May-2003

**Printed:** 20-Mar-2007

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# 3 SYNOPSIS

<table>
<thead>
<tr>
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<tr>
<td>Calcipotriol plus betamethasone dipropionate</td>
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**Title of study/Protocol Code Number:**

In vivo bioequivalence study of betamethasone dipropionate in DAIVOBET/DOVOBET gel and DIPROSONE ointment according to FDA Guideline for vasoconstrictor bioassay.

**International Co-ordinating Investigator:**

[Redacted], MD

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<th>Centre details:</th>
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**Publication references:**

No publication planned

**Study period details:**

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<th>Pilot Phase:</th>
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<tbody>
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<td>First subject enrolled on 07 March 2005</td>
<td>First subject enrolled on 02 May 2005</td>
</tr>
<tr>
<td>Last subject completed on 18 March 2005</td>
<td>Last subject completed on 17 June 2005</td>
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</table>

**Phase of development:**

Phase I/IIa

(pharmacodynamic study)

**Objectives/hypothesis, if applicable:**

This study comprised two parts:

The pilot phase of this study was intended to determine the dose duration response curve for the commercially available reference product, DIPROSONE ointment (betamethasone dipropionate 0.5mg/g, Schering Plough), in order to estimate the dose duration ED<sub>50</sub> to be used in the pivotal phase (part II of this study) and the proportion of subjects expected to meet a posteriori detector criterion based on the D<sub>2</sub>/D<sub>1</sub> ratio.

The pivotal phase of this study was intended to compare the pharmacodynamic activity (skin blanching effect due to vasoconstriction) of DAIVOBET/DOVOBET gel (formulation
containing betamethasone dipropionate 0.5mg/ml and calcipotriol 50mcg/g) to the commercially available reference product DIPROSONE ointment in order to document the in vivo bioequivalence of the DAIVOBET/DOVOBET gel formulation to the reference product.

**Study methodology:**

**Design**

The study was a single centre, randomised, controlled, investigator blinded, dose duration response study with randomisation of dose duration to skin sites and intra-individual comparison of treatments.

The study was conducted as an unoccluded Mc Kenzie-Stoughton’s test (human skin blanching assay) with staggered application and synchronised removal, colorimetric measurements and visual scoring to evaluate skin blanching.

**Pilot Phase**

Within 15 days prior to the test a screening visit to select responder subjects meeting a predefined minimum vasoconstrictor response to DIPROSONE ointment was performed. On the day of the test a baseline colorimetric measurement was performed. Eight dose durations of DIPROSONE ointment (0.25, 0.5, 0.75, 1, 1.5, 2, 4 and 6 hours) were applied to test sites on the forearms. Colorimetric measurements and visual scoring were performed 10 min, 2, 4, 6, 19 and 24 hours after product removal.

**Pivotal Phase**

Within 15 days prior to the test a screening visit to select responder subjects meeting a predefined minimum vasoconstrictor response to DIPROSONE ointment was performed. On the day of the test a baseline colorimetric measurement was performed. DAIVOBET/DOVOBET gel was applied with dose duration ED$_{50}$ to two test sites per forearm and DIPROSONE ointment was applied with dose duration ED$_{50}$ to two test sites, dose duration D$_1$ to one site and dose duration D$_2$ to one site per forearm. Colorimetric measurements and visual scoring were performed 10 min, 2, 4, 6, 19 and 24 hours after product removal.
Name of Sponsor/Manufacturer: LEO Pharma A/S

Location of study report in Regulatory Dossier for authorities (For National Authority Use only)

Name of Investigational Product/Finished Product, if available: DAIVOBET/DOVOBET gel

Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Evaluation criteria

Primary criterion
Colorimetric measurements: At each time point, two successive series of measures were performed on each test site. The primary efficacy variable was the a* value which represents the red/green balance.

Secondary criterion
Visual skin blanching assessment (visual score (VS)) was performed by two independent readers, using the following scale:

0 no change in skin colour
1 slight (barely visible) blanching
2 obvious blanching
3 intense blanching
4 blanching judged to be maximal

Intermediate scores (of half unit) could be used when needed.

Safety criteria
Clinical assessment of local irritation signs and adverse events were reported on an ongoing basis.

Number of subjects enrolled:

Pilot phase:
Eighteen healthy subjects were enrolled and 12 subjects who met the "responder" criteria defined in the FDA guideline were randomised.

Pivotal phase:
Ninety-five healthy subjects were enrolled and 70 subjects who met the "responder" criteria defined in the FDA guideline were randomised.
<table>
<thead>
<tr>
<th>Name of Sponsor/Manufacturer:</th>
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<td>LEO Pharma A/S</td>
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</tr>
<tr>
<td>DAVOBET/DOVOBET gel</td>
<td>Page:</td>
<td></td>
</tr>
<tr>
<td>Name of Active Substance:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriol plus betamethasone dipropionate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis and main criteria for subject selection:**

Healthy subjects of either sex, 18 to 45 years old, with a skin type I to IV and demonstrating adequate vasoconstriction to DIPROSONE ointment (unoccluded application of the reference for 4-6 hours screening pre-test showing a visual score of at least one unit (visual scale (0-4)).

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

**Investigational product:** DAVOBET/DOVOBET gel,
Batch number 042596101/Exp. 08/2006.

**Pilot Phase:**
No Investigational product was applied in the pilot study.

**Pivotal Phase:**
Single application of 10 ml on four different test sites (2 sites per arm) at a dose duration corresponding to approximately ED₅₀ (determined in the pilot study).

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

**Reference product:** DIPROSONE ointment,
Batch number 4015/Exp. 09/2007.

**Pilot Phase:**
10 ml single applications of the reference product, DIPROSONE ointment, were applied under non-occluded conditions on eight different test sites (eight different dose durations, from 0.25 hour to a maximum of 6 hours were tested).

**Pivotal Phase:** Single applications of 10 ml were applied on 4 different test sites (two per arm) for dose duration of approximately ED₅₀, 2 sites (one per arm) for dose duration D₁ (approximately 0.25-0.5 times the ED₅₀) and 2 sites (one per arm) for dose duration of D₂ (approximately 2-4 times the ED₅₀).
Name of Sponsor/Manufacturer: LEO Pharma A/S

Name of Investigational Product/Finished Product, if available: DAIVOBE T/DOVOBET gel

Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Location of study report in Regulatory Dossier for authorities

Volume:

Page:

Pilot Phase: 10μl single application under non-occluded conditions on eight different test sites dose durations, with maximum dose duration of 6 hours.

Pivotal Phase: The test product (DAIVOBE T/DOVOBET gel) was applied on four sites for duration equal to ED50. DIPROSONE ointment was applied on eight sites for durations equal to D1 (two sites), to ED50 (four sites) and to D2 (two sites).

According to the FDA guidance, the pivotal study was performed with the ED50 value determined in the pilot study. The determination of D1 and D2 was based on the ED50 value.

Statistical methodology:

Population to be analysed: All subjects in the Safety Analysis Set for safety. Per protocol analysis set for pharmacodynamics.

Variables to be analysed:

- Primary criterion:
  Colorimetric parameter a*. The analysed variable was the mean of the two successive measurements performed on each site. For each time point, colorimetric variables was adjusted to baseline and to untreated controls on the same forearm (Δa*).

- Secondary criterion:
  Visual score of skin blanching (from 0 to 4). The analysed variable was the mean of visual blanching scores between the two readers, for each time.

Methods:

The area under the effect curve (AUEC0-24h) over 24 hours was calculated for Δa* (adjusted values) using the classical trapezoidal method for each individual test site.

Bioequivalence was estimated on the pivotal per protocol analysis set using Locke’s method for calculating the 90% confidence interval for the ratio of average AUEC0-24h (model of FDA guideline).
Pilot Phase

Eighteen subjects attended the screening visit and were enrolled in the pilot phase. Six were not “responders” and were discarded.

Twelve positive responder subjects (8 females, 4 males) aged 23-40 years (mean: 30.9 ± 5.9) were randomised and completed the study.

The ED50 estimated from Emax model fitted by nonlinear least squares regression was equal to 0.24 h (14 min), D1 to 0.12 h (7 min) and D2 to 0.48 h (29 min).

For practical reasons, the values used in the pivotal phase were: ED50 = 20 min., D1 = 5 min. and D2 = 60 min.

Pivotal Phase

Ninety-five healthy subjects attended the screening visit and were enrolled in the pivotal phase. Twenty-four were not “responders” and one subject was discarded as he was late for the randomisation visit.

Seventy positive responder subjects (58 females, 12 males) aged 19-41 years (mean: 28.0 ± 5.7) were randomised and completed the study.

Under the conditions of the study, 27 out of the 70 subjects enrolled were found “detectors” according to the FDA guidelines and were analysed for bioequivalence.

The Mean AUEC0-24h for Δн* (baseline adjusted and untreated control site corrected) by treatment are reported in the table below for the per protocol analysis set:

<table>
<thead>
<tr>
<th></th>
<th>DAIVOBET/DOVOBET gel</th>
<th>DIPROSONE ointment</th>
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</thead>
<tbody>
<tr>
<td>N (1)</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>Mean</td>
<td>-10.03</td>
<td>-12.89</td>
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<tr>
<td>Std</td>
<td>10.87</td>
<td>12.87</td>
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<tr>
<td>Min</td>
<td>-44.77</td>
<td>-59.14</td>
</tr>
<tr>
<td>Max</td>
<td>15.89</td>
<td>25.07</td>
</tr>
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</table>

(1) Number of sites

At a dose duration of 20 minutes (ED50) determined from the pilot study
DAIVOBET/DOVOBET gel was found not to be bioequivalent to DIPROSONE ointment as the 90% confidence interval for the main criterion (AUEC0-24h for baseline and untreated site colorimetric adjusted parameter a*) was 64-95%. This result is not within the limit of 80-125% defined by the FDA for determination of bioequivalence.

The results obtained on the secondary criterion (visual score of blanching) also demonstrated that DAIVOBET/DOVOBET gel is not bioequivalent to the reference formulation.

<table>
<thead>
<tr>
<th>DAI\nobET/DOVO\nbET gel</th>
<th>DIPROSONE ointment</th>
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<td>ED50</td>
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<tr>
<td>D4</td>
<td>24.3</td>
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</table>

(1) Number of sites

No signs of local irritation were reported. In the pivotal phase, a total of two mild adverse events were reported by one subject: one common cold (unrelated) and one urticaria flare outside the tests areas (possibly related).

No serious adverse event was reported.

Under the conditions of the study, DAIVOBET/DOVOBET gel and DIPROSONE ointment were safe and well tolerated.

Conclusion:

The study was conclusive and demonstrated that DAIVOBET/DOVOBET gel was not bioequivalent to DIPROSONE ointment regarding AUEC0-24h for the colorimetric parameter Δa* (baseline adjusted and untreated control site corrected).

DAIVOBET/DOVOBET gel induced less skin blanching than DIPROSONE ointment, suggesting that DAIVOBET/DOVOBET gel can be considered as a weaker (clinically less potent) topical corticosteroid than DIPROSONE ointment.

Report date:

20-MAR-2007
### 3.1 Schedule/Chart of Study Procedures

#### Pilot phase – Flow chart

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<td><strong>Application Phase</strong></td>
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<td>T-4h</td>
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(1) Female subjects of child bearing potential. Result had to be negative to continue in the study.
(2) According to the randomisation scheme.
(3) Baseline colorimetric measurements had to be performed on all 12 test sites within one hour prior to first drug application (T0 – 6h).
(4) PR: Product Removal
(5) FU: If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit.
### Pivotal phase - Flow chart

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<td>Concomitant medication</td>
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<td>X</td>
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</tbody>
</table>

\(^{1}\) Female subjects of child bearing potential. Result had to be negative to continue the study.

\(^{2}\) According to the randomisation scheme.

\(^{3}\) Baseline colorimetric measurements had to be performed on all 16 test sites within one hour prior to first drug application (T0 – D1).

\(^{4}\) PR: Product Removal

\(^{5}\) FU: If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit.
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## 5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

### 5.1 LIST OF ABBREVIATIONS

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<tr>
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>AFSSAPS</td>
<td>Agence Française de Sécurité Sanitaire des Produits de Santé (French Health Agency)</td>
</tr>
<tr>
<td>AUEC_{0.24h}</td>
<td>Area Under the Effect Curve</td>
</tr>
<tr>
<td>BMD</td>
<td>Betamethasone Dipropionate</td>
</tr>
<tr>
<td>CCPRPB</td>
<td>Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (Consultative Committee for the Protection of Persons in the Biomedical Research)</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FU</td>
<td>Follow-up</td>
</tr>
<tr>
<td>CIE</td>
<td>Commission Internationale de l'Eclairage</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>D_1</td>
<td>Dose duration corresponding to approximately half ED_{50}</td>
</tr>
<tr>
<td>D_2</td>
<td>Dose duration corresponding to approximately two ED_{50}</td>
</tr>
<tr>
<td>ED_{50}</td>
<td>Dose duration corresponding to approximately half maximal blanching response</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>ICTM</td>
<td>International Clinical Trial Manager</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>LEO</td>
<td>LEO Pharma</td>
</tr>
<tr>
<td>MD</td>
<td>Medical Doctor</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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5.2 DEFINITION OF TERMS

Day-1 is defined as the day immediately before the day of the first product application.
Day 1 is the day of the first application.
Day 0 is not used in this study.
Time zero (T0) equals time of synchronised drug product removal on Day 1.

Responder: A “responder” subject is a subject who shows a visual reading of at least one unit two hours after dose duration of 4-6 hours during the screening period.
Detector: A “detector” subject is a subject whose AUEC$_{0-24h}$ values at D$_1$ and D$_2$ are both negative and who meets the following criterion:

\[
\frac{\text{AUEC}_{0-24h} \text{ at } D_2}{\text{AUEC}_{0-24h} \text{ at } D_1} \geq 1.25
\]

Terms defined by ICH Guidelines are not mentioned here.

**Assessment**
A (cluster of) characteristic(s) measured and/or recorded for a patient.

**Concomitant Medication**
Any medication taken by a subject apart from the investigational product(s).

**Enrolled Subject**
A patient/subject for whom informed consent has been obtained and a CRF number assigned.

**Fraud**
Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers’ results, unwarranted authorship, and misleading application for positions or funds.

**International Clinical Trial Manager (ICTM) (formerly PCPC)**
The person appointed by LEO to be the main international representative responsible for all aspects of a clinical trial.

**Investigator Agreement**
A contract between LEO and an investigator specifying the conditions for the co-operation in the clinical trial and the investigators’ responsibilities.

---

1 Area Under the Effect Curve
**Investigator Staff Signature Form**
A form on which subinvestigators and other trial-related site staff sign and date and the Investigator authorises their trial-related tasks/duties.

**Investigator Trial File**
The collection of trial documents required by LEO GCP SOPs, ICH Guidelines and/or regulatory requirements to be on file at the investigator site.

**LEO**
LEO (no suffix): Refers to the corporate organisation of LEO Pharma.

**Local Clinical Project Co-ordinator (LCPC)**
The person appointed by LEO to be the national representative responsible for all aspects of a clinical trial within a country.

**Monitor**
A person appointed by LEO to carry out monitoring of a clinical trial.

**National Clinical Trial Manager (NCTM) (formerly LCPC)**
The person appointed by LEO to be the national representative responsible for all aspects of a clinical trial within a country.

**Principal Clinical Project Co-ordinator (PCPC)**
The person appointed by LEO to be the main international representative responsible for all aspects of a clinical trial.

**Randomisation Code List**
A list of (sequential) numbers to each of which a treatment is allocated (assigned). Treatment may be revealed as a code letter (e.g., A, B, ...) or by directly revealing the specific treatment (investigational product, e.g., Calcipotriol ointment).
Response Criterion
An assessment or a transformation of the assessment(s) described on a patient level, for which a statistical analysis is performed, i.e., a P-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.

Subject Identification List
A summary list kept by the investigator in the Investigator Trial File that records the names of all subjects enrolled and the date of enrolment in the trial at that centre, with the subject’s corresponding CRF Book Number, to allow the investigator/institution to reveal the identity of any subject, if required.

Subject Screening Log
A document kept by the investigator which identifies patients/subjects who entered pre-trial screening.

Subject Study Card
A card given to a subject by the trial centre at the time trial medication is first dispensed to a subject, to identify that the subject is receiving treatment with an investigational product.

Treatment Code Envelope
A sealed letter/envelope containing the identification of an individual subject’s treatment/investigational product(s).
6 ETHICS

6.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The protocol and any relevant amendments were approved by/received favourable opinion from relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) on 4 February, 2005.

The IEC/IRB consulted and a copy of the approval/favourable opinion is given in Appendix VI.

The appropriate Regulatory Authority(ies) was notified of/approved the trial, as required.

6.2 ETHICAL CONDUCT OF THE STUDY

The trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments.

The trial was conducted in accordance with the principles of GCP.

6.3 PATIENT INFORMATION AND INFORMED CONSENT

All healthy subjects in this study received written and verbal information concerning the study (subject’s written information), approved by the CCPPRB. This was supplied by the Investigator, Sub-Investigator or designated staff and was understood and signed by each healthy subject prior to his/her inclusion in the study. This information emphasised that participation in the study was voluntary and that the healthy subject could withdraw from the study at any time and for any reason. All healthy subjects were given opportunity to ask questions and were given sufficient time to consider before consenting.

The healthy subjects (or their legally acceptable representative and/or witness, as applicable), were asked to consent that data are recorded, collected, processed and may be transferred to EU and non-EU countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

All investigators signed an “investigator’s agreement” to confirm the above.
A representative subject information sheet and informed consent form is provided in Appendix V.

7 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

7.1 REPORT AUTHOR(S)

[Redacted]

PhD Mathematical Statistics, MSc Math, Biostatistics Department, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

[Redacted]

MSc Stat, Biostatistics Department, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark.

7.2 INVESTIGATORS, TRIAL CENTRES AND CROS

7.2.1 International Co-ordinating Investigator

The International Co-ordinating Investigator was responsible for approval of the protocol, CRF and study report, on behalf of all investigators, and as agreed to in an International Co-ordinating Investigator Agreement.

[Redacted], MD, France.

7.2.2 National Co-ordinating Investigators

The investigator below was responsible for national issues relating to the study as agreed to in the National Co-ordinating Investigator Agreement.

[Redacted], MD, France.
7.2.3 **Investigators**

Each participating investigator was responsible for all aspects of the trial conduct at his/her site, and as agreed to in an Investigator Agreement signed prior to trial initiation.

If subinvestigators were delegated trial related tasks/duties, this was documented on the Investigator Staff Signature Form. The complete list of all participating investigators and (sub)investigators is provided in Appendix VII and Appendix VIII.

7.2.4 **Contract Research Organisation(s)**

Not applicable for this study.

7.2.5 **Data Monitoring Committees**

Not applicable.

7.3 **COMPANY PERSONNEL**

On behalf of LEO, only the Medical Director, Medical Department, LEO DK, the Head of Biostatistics Department, LEO DK, and the Vice President, Medical Director, LEO, were authorised to approve the Protocol and any subsequent Protocol Amendments.

7.3.1 **International Clinical Trial Manager (ICTM)**

[Redacted]
Clinical Operations, LEO Pharma, Industri parken 55, DK-2750 Ballerup, Denmark

7.3.2 **National Clinical Trial Manager (NCTM)**

[Redacted], MD, [Redacted], LEO Pharma, BP 311, F-78054 St. Quentin Yvelines Cedex, France

7.3.3 **Sponsor’s Medical Expert**

[Redacted], MD, [Redacted], LEO Pharma, Industri parken 55, DK-2750 Ballerup, Denmark
7.3.4 Study Statistician

**[Redacted]**, MSc Stat, Biostatistics Department, LEO Pharma A/S, Industrieparken 55, DK-2750 Ballerup, Denmark.

7.3.5 Medical Director Drug Safety, LEO

**[Redacted]**, MD, Drug Safety Department, LEO Pharma, Industrieparken 55, DK-2750 Ballerup, Denmark.

### 8 INSURANCE AND LIABILITY

The subjects in the present 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 July 1996.
9 INTRODUCTION AND RATIONALE

9.1 BACKGROUND AND INVESTIGATIONAL PRODUCTS
Psoriasis vulgaris is a very common dermatological disorder, consisting of both skin inflammation and skin hyperproliferation. The prevalence of psoriasis is 1-3% of the European and US population. Most of the subjects are treated with topical treatments alone.

The two most frequently used topical therapeutics for psoriasis vulgaris are topical corticosteroids and topical vitamin D derivatives. Corticosteroids affect mainly the inflammatory processes, while vitamin D analogues are involved in the moderation of keratinocyte differentiation and proliferation. Topical corticosteroids are very effective but their long term usage must be restricted due to their well known adverse reactions such as skin atrophy and early relapse. Vitamin D derivatives have been shown to be active on the hyperproliferative component but in many cases do not suppress totally the skin inflammation.

Clinical trials have demonstrated that the two treatments used in a combination regimen are more effective than either agent used as monotherapy. A new formulation (DAIVOBET/DOVOBET ointment) was shown to be superior in terms of efficacy to each individual component used alone, either in the DAIVOBET/DOVOBET ointment vehicle (3) or in a marketed formulation (DAIVONEX/DOVONEX and DIPROSONE, respectively) (4). The safety profile of DAIVOBET/DOVOBET was shown to be better than that of calcipotriol alone and comparable to that of betamethasone alone (4, 5).

In order to demonstrate equivalence, clinical trials are in principle necessary but other models may be used. For this purpose, human pharmacodynamic studies can be considered provided that the model is validated. For topical corticosteroids, a model using the human skin blanching assay (1) has been validated by the FDA and guidance issued on 2 June 1995 (10).

The human skin blanching assay (vasoconstriction test) described by R. Stoughton and A.W. Mc Kenzie in 1962 (1) has been used for many years by pharmaceutical companies and was accepted by the Food and Drug Administration as a mean to predict the clinical potency of topical corticosteroid formulations. This assay was based on the property of corticosteroids to produce blanching or vasoconstriction in the microvasculature of the skin. The performance of the test was optimised using visual scoring and colorimetric measurement that provides quantitative assessment of the skin blanching (6, 7).
In most cases, the results from the skin blanching assays correlate well with results from clinical controlled studies performed in psoriasis (8). Based on skin blanching assays and comparative clinical trials, topical glucocorticoids have been classified in Europe into four potency classes (WHO potency groups), in order of their increasing potency (9).

The vasoconstriction test was first used for ranking new formulations within the efficacy spectrum of topical corticosteroids (mild to very potent). Then, its usage was extended to demonstrate the bioequivalence ("pharmacodynamic" equivalence) of a generic product versus the innovator.

9.2 STUDY RATIONALE

DAIVOBET/DOVOBET ointment is a combination of betamethasone dipropionate and calcipotriol marketed by LEO Pharma which proved to be bioequivalent to DIPROSONE ointment within a previous study (12). LEO Pharma is presently developing a new DAIVOBET/DOVOBET gel formulation.

The aim of the study was to establish potency of DAIVOBET/DOVOBET gel using the model according to FDA’s Guidance for Industry: “Topical Dermatologic corticosteroids: in vivo bioequivalence”.

The guidance has suggested conducting two in vivo studies – a pilot dose duration-response study and a pivotal in vivo bioequivalence study comparing test and reference products. The pilot study characterised the dose duration response relationship for the drug in terms of the E\text{max} model and was conducted solely with the reference listed drug (DIPROSONE ointment (a WHO group III corticosteroid) for the present study). The comparison of test and reference products in the pivotal study was conducted at a dose duration approximately equal to the population ED\text{50} (dose duration corresponding to approximately half maximal blanching response) determined in the pilot study. Sensitivity in the pivotal study was established through dosing the reference product calibrators at two dose durations, D\text{1} (the dose duration corresponding to approximately half (0.25-0.5 times) ED\text{50}) and D\text{2} (the dose duration corresponding to approximately two (2-4 times) ED\text{50}) determined from the pilot study.

Therefore, the present study was conducted in two parts: the first part was the pilot study and was performed only with the reference formulation, DIPROSONE ointment (Schering-Plough), whereas the second part, the pivotal study, was performed after the first one in order to demonstrate the in vivo bioequivalence of DAIVOBET/DOVOBET gel to the reference
DIPROSONE ointment. The design of the pivotal study was based on the result of the pilot study.

10 STUDY OBJECTIVES

10.1 PRIMARY OBJECTIVE
The pilot phase of this study was intended to determine the dose duration response curve for the commercially available reference product, DIPROSONE ointment, in order to estimate the dose duration $ED_{50}$ to be used in the pivotal in vivo bioequivalence study (part II of the study) and the proportion of subjects expected to meet the “detector” criterion based on $D_1$ and $D_2$.

The pivotal phase of this study was intended to compare the pharmacodynamic activity (skin blanching effect due to vasoconstriction) of DAIVOBET/DOVOBET gel (formulation containing betamethasone dipropionate and calcipotriol) to the commercially available reference product DIPROSONE ointment in order to document the in vivo bio-equivalence of the DAIVOBET/DOVOBET gel formulation to the reference product.

10.2 SECONDARY OBJECTIVES
To assess the overall tolerability of the trial products in both the pilot phase and the pivotal phase of the study.
11 INVESTIGATIONAL PLAN

The entire Study Protocol is presented in Appendix I and the CRF Book is presented in Appendix II.

11.1 STUDY DESIGN

The study was a single centre, randomised (application sites), controlled, investigator blinded, intra-subject comparison study.

Pilot Phase

This was a dose duration-response study based on the reference product only (DIPROSONE ointment) with randomisation of eight different dose durations to eight test sites. Two sites per forearm were left untreated as control sites. The screening of the subjects was performed at the within the 15 days prior to the application phase and allowed checking the compatibility with the inclusion and exclusion criteria. During the screening visit, physical examination, and vital sign measurements were carried out. A screening test was performed with the reference product (test site different from the forearm) in order to evaluate the individual blanching response (responder criteria).

On Day 1, after carrying out checking of the inclusion/exclusion criteria, the investigator delimited 12 sites (2.2 cm diameter) on the anterior side of the forearms (6 sites per forearm). For all sites, a baseline colorimetric evaluation was performed prior to the first drug application (i.e. within one hour before T0 minus 6 hours).

The study was performed with staggered applications and synchronised removal: The study treatment was applied to skin sites at eight different times (8 dose durations) and was removed at the same time for all dose durations (T0).

Eight different dose durations from 0.25 to 6 hours were tested. Untreated control sites (2 on each forearm) enabled to correct the active drug skin sites for spontaneous circadian color changes during the study unrelated to drug exposure. Application to each subject of the 8 dose durations and 4 untreated sites were done according to a randomised application list without the presence of the 2 evaluators/readers.

After drug removal (T0), skin blanching assessment was performed both subjectively using a 5-point (0-4) visual assessment scale and objectively with the Minolta CR 300 Chromameter (7, 8) over a 24h period: 10 min, 2, 4 and 6 hours after the drug removal on Day 1; and 19 and 24 hours after drug removal on Day 2. The dose duration corresponding to half maximal response (ED\textsubscript{50}) was determined. Then, determination of D\textsubscript{1} and D\textsubscript{2} was performed.
Pivotal Phase
The study phase was a pharmacodynamic bioequivalence study using within-study day replicate single dose durations of test and reference products, based on the population ED50 identified in the pilot phase.

Individual subject dose duration-response was based upon an acceptable D2/D1 ratio of AUEC0-24h values of the reference drug. The minimum value of the ratio should be 1.25.

Success in meeting this dose duration was determined through duplicate dosing of the reference product at D1, the dose duration equal to approximately 0.25-0.5 times the population ED50 and at D2, the dose duration equal to approximately 2-4 times the population ED50.

The number of subjects to be included in the pivotal phase were more precisely defined after the analysis of the pilot part had been completed. Forty to sixty evaluable subjects i.e. subjects who meet the “responder” and “detector” criteria were required for the study.

Seventy subjects were included in the pivotal phase.

A “responder” subject is a subject who shows a visual reading of at least one unit two hours after dose duration of 4-6 hours during the screening period.

A “detector” subject is a subject whose AUEC0-24h value at D1 and D2 are both negative and that meets the following criterion:

\[
\frac{AUEC_{0-24h} \text{ at } D2}{AUEC_{0-24h} \text{ at } D1} \geq 1.25
\]

The screening of the subjects was performed at the within the 15 days prior to the first study drug application and allowed checking the compatibility with the inclusion and exclusion criteria. During the screening visit, a physical examination and a vital sign measurement was carried out. A screening test was performed with the reference product (test site different from the forearm) in order to evaluate the individual blanching response.

On Day 1, after carrying out checking of the inclusion/exclusion criteria, the investigator delimited 16 sites (2.2 cm diameter) on the anterior side of the forearms (8 sites per forearm). For all sites, a baseline colorimetric evaluation was performed prior to the first drug application (i.e. within one hour before T0 minus D2).

The study was performed with staggered applications and synchronized removal: the study treatment was applied to skin sites at different times (D2, ED50 and D1 dose durations) and was removed at the same time for all dose duration (T0). Untreated control sites (2 on each forearm) enabled to correct the active drug skin sites for spontaneous circadian color changes during the study unrelated to drug exposure. Applications of the study drugs to each subject were done according to a randomised application list without the presence of both evaluators/readers.
After drug removal (T0), skin blanching assessment was performed both subjectively using a 5-point (0-4) visual assessment scale and objectively with the Minolta CR 300 Chromameter (7, 8) over a 24h period: 10 min, 2, 4 and 6 hours after the drug removal on Day 1 and 19 and 24 hours after drug removal on Day 2.

11.2 TIME SCHEDULE
Planned start of clinical phase: February 2005
Planned end of study: June 2005

11.3 NUMBER OF PATIENTS/SAMPLE SIZE
Twelve healthy subjects who met the “responder” criteria were to be included in the pilot phase.
Approximately 90 healthy subjects were to be enrolled in order to have 40-60 evaluable subjects who met the “responder” and “detector” criteria randomised in the pivotal phase.

11.4 CRITERIA FOR PATIENT SELECTION (IN- AND EXCLUSION)

11.4.1 Inclusion Criteria
1. Following receipt of verbal and written information about the trial, the subject had to provide signed and dated informed consent before any trial related activity was carried out.
2. Healthy male or female subjects, 18 to 45 years old, both inclusive, with skin type I to IV according to the Fitzpatrick scale (11).
3. Subjects defined as “responders” demonstrating adequate vasoconstriction to the reference product (un-occluded application of the reference ointment for 4-6 hours must show a visual score of at least one unit (visual scale (0-4)).
4. Female healthy subjects of childbearing potential had to use a reliable contraceptive method (oral contraceptive pill, intrauterine device, bilateral tuballigation, condoms) at least two months before the start of the study and had to accept to continue this method during the study; or of non childbearing potential i.e., post-menopausal (one year without menstrual period, hysterectomy or bilateral ovariectomy).
5. Non smoker subjects.
6. Healthy subjects willing to follow the study restrictions and complete the study.
11.4.2 Exclusion Criteria

1. Females who were pregnant, breast feeding or who were planning a pregnancy during the course of the trial.
2. Females of child-bearing potential with positive urine pregnancy test at screening (before the screening test for evaluation of the blanching response was carried out).
3. Abnormal pigmentation of the skin, that could, in any way, confound interpretation of the study results.
4. Any systemic or cutaneous disease that could in any way confound interpretation of the study results (e.g. atopic dermatitis, contact eczema, or psoriasis).
5. Known or suspected sensitivity related to any component of any of the formulations being tested (see ingredients listed in the Investigator's Brochure).
6. Involvement in any investigational protocol (drug or device) within 3 months prior to the study.
7. Healthy subjects who were in the exclusion period in the Healthy National Register of the French Ministry of Health (10).
8. Healthy subjects protected by the Law (prisoners, guardian ships).
9. Use of:
   - Topical dermatologic drug therapy on ventral forearms, including prior dosing of a topical corticosteroids in a pharmacodynamic study to particular skin site within one month prior to enrolment.
   - Systemic drugs which may interfere with the blanching reaction including, but not limited to corticosteroids and other vasoactive (constrictor or dilator) medication (nitrate derivatives, antihypertensives, antihistamine, phenylpropanolamine, diphenhydramine, NSAIDs, pseudo-ephedrine etc), within two weeks prior to enrolment.
   - Any other medication which would interfere with the study results.
10. Subjects hospitalised in a Public or Private Establishment for a reason other than participation in the Research.
11. Clinically significant hypertension or circulatory disease.
12. Caffeine intake greater than 500 mg per day prior or during the study.
13. Persons who require shaving on ventral forearms to insure consistent dose on skin surface.
14. Any obvious difference in skin color between arms.
15. Clinically significant history of alcoholism or drug abuse.

11.4.3 Subject Screening Log

First, the subject was informed about the study and signed a consent form. Each subject who had signed the informed consent form was registered on a Subject Screening Log.
11.4.4 Subject Registration

At screening, each subject was assigned a CRF Book Number. This number was pre-printed on each copy of each page on the Case Report Form used for that subject.

11.5 WITHDRAWAL CRITERIA

Subjects could be withdrawn for any of the following reasons:

1. Voluntary withdrawal: Subjects were free to withdraw from the study at any time and for any reason.
2. Medical reasons: The investigator was free to withdraw the subject at any time for medical reasons.
3. Adverse events: Any adverse event that the investigator or the subject considered unacceptable.
4. Exclusion criteria: Any exclusion criteria that emerged/became apparent during the subject’s participation in the study.

Reason(s) for withdrawal were to be recorded in the Case Report Form.

Subjects withdrawn were not to be substituted.

Subjects discovered, after enrolment/randomisation, not to have fulfilled all in/exclusion criteria at time of enrolment, were to be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, found withdrawal inappropriate. The final assessment (at the correct scheduled time) was, however, to be attempted to be completed for all subjects.

Such deviation(s) from the protocol were to be reported to LEO (and IEC/IRB, as appropriate) and written in the Study Report.

11.6 INVESTIGATIONAL PRODUCTS

<table>
<thead>
<tr>
<th>Brand name/name investigational product</th>
<th>DAIVOBET/DOVOBET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>Gel</td>
</tr>
<tr>
<td>Active ingredient name/concentration</td>
<td>Betamethasone 0.5 mg/g (as dipropionate) and calcipotriol 50 mcg/g</td>
</tr>
<tr>
<td>Excipients</td>
<td>Castor oil, hydrogenated polyoxypropylene-15-stearyl ether, paraffin</td>
</tr>
<tr>
<td>Pack size(s)</td>
<td>50 g in a 120 ml bottle</td>
</tr>
<tr>
<td>Manufacturer’s name</td>
<td>LEO Pharma</td>
</tr>
<tr>
<td>Supplier’s name</td>
<td>LEO Pharma</td>
</tr>
<tr>
<td>Certifier’s name</td>
<td>LEO Pharma</td>
</tr>
<tr>
<td>Lot number(s)/expiry date(s)</td>
<td>04259601/Exp. 08/2006</td>
</tr>
</tbody>
</table>
Brand name/investigational product | DIPROSONE
---|---
Formulation | Ointment
Active ingredient name/concentration | Betamethasone 0.5 mg/g (as dipropionate)
Excipients | White soft paraffin, liquid paraffin
Pack size(s) | 30 g commercial tube
Manufacturer’s name | Schering Plough
Supplier’s name | LEO Pharma
Certifier’s name | LEO Pharma
Lot number(s)/expiry date(s) | 4015 / Exp. 09/2007

### 11.6.1 Administration of Investigational Products

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Topical on the volar part of the forearms</th>
</tr>
</thead>
</table>
| Dosing range | **Pilot Phase:**
10 mcl of DIPROSONE applied under non-occlusion conditions

**Pivotal Phase:**
10 mcl of DAIVOBEI/DOVOBEI applied under non-occlusion conditions
10 mcl of DIPROSONE applied under non-occlusion conditions

| Dosing frequency | **Pilot Phase:**
10 mcl applied on eight different test sites (dose durations: 6, 4, 2, 1.5, 1, 0.75, 0.5 and 0.25 hour).

**Pivotal Phase:**
The test product (DAIVOBEI/DOVOBEI gel) applied on four sites for duration equal to EDs0. DIPROSONE ointment applied on eight sites for durations equal to D1 (two sites), to EDs0 (four sites) and to D2 (two sites).
11.6.2 Treatment Assignment

Allocation of treatment: Subjects who were found to be in compliance with all the protocol inclusion and exclusion criteria were randomised sequentially in the order in which the subjects have been enrolled at Day 1. Treatment assignment was pre-planned according to a computer generated randomisation schedule.

Test Site Scheme – Pilot Phase

Hours before Drug Removal (Pilot Phase)
11.6.2.1 Randomisation Code List
During the trial, only three copies of the Randomisation Code List were kept: one with the Investigational Product Packaging Supervisor, LEO and the other with the R&D, Quality Assurance Department, LEO. The third list was kept at the investigator’s site. These lists were kept inaccessible to all persons involved with conduct/administration of the trial.

11.6.3 Blinding of Study
The investigator/evaluator was blinded to the identification of the treatment application of drug product. Thus, product application and product removal were performed by a third person. In addition, access to the randomisation list was limited to the designated third person responsible for product application.

11.6.4 Breaking the Randomisation Application List
Until each part of the study was unblinded the relevant randomisation application list was only kept in three copies: one with the Investigational Product Packaging Manager and one with the R&D Quality Assurance Department, LEO Pharma. The third randomisation application list was kept by a designated person responsible for drug product application and removal. This list was kept inaccessible for the investigator/evaluator who was kept blinded to the identification of the treatment application throughout the trial.
11.6.4.1 Unblinding of Individual Patient Treatment
The investigator/pharmacist and the sponsor held a copy of the treatment allocation for each patient in an individual sealed treatment code envelope. The envelope had the randomisation code number on the outside and gave the identity of the investigational product inside.

The code was only to be broken in an emergency where investigational product identification was necessary. In such an event, the date and the reason for opening the envelope was to be recorded on the appropriate page in the Case Report Form Book. Additionally, the following information was to be recorded directly on the outside of the envelope:

Date of opening  
Reason for opening  
Opened by  
Date of re-sealing

Any opened treatment code envelope was to be re-sealed as soon as possible after opening.

All treatment code envelopes originally delivered to the centre by LEO were collected and accounted for by the trial monitor at the end of the trial. All treatment code envelopes were collected and accounted for by LEO prior to unblinding the trial.

11.6.4.2 Unblinding of the Study
The trial was fully unblinded only when a final validated database was available, the Statistical Analysis Plan had been approved and all envelopes were accounted for with specific attention to opened envelopes prior to unblinding.

The QA Department R&D, LEO, acknowledged the accountability of individual treatment code envelopes before the blind was broken.

Apart from the application list only two copies of the randomisation code list were kept during the study: one original with the Investigational Product Packaging Supervisor and a copy with the QA Department, R&D, LEO. Both copies were kept in a locked place.
11.6.5 Drug Accountability and Compliance Checks
Upon receipt of the clinical supplies, the designated study personnel conducted a complete inventory of all investigational and control products, completed and returned the Investigational Product Delivered Form together with the temperature records to LEO Pharma and assumed responsibility for storage and dispensing of the investigational and reference products. In accordance with ICH GCP guideline, the Investigator or the designated study personnel agreed to keep the Investigational Products in a secure location with restricted access.

11.6.6 Prior and Concomitant Treatment
Use of concomitant treatment was to be recorded in the subject’s medical record and the CRF (drug name, total dose, indication and dates of start and stop).
### 11.7 STUDY PROCEDURES

**11.7.1 Schedule of Study Procedures – Pilot Phase**

<table>
<thead>
<tr>
<th>Day-15 to Day-1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Application Phase</td>
<td>PR&lt;sup&gt;(a)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Screening visits</td>
<td>Before 1&lt;sup&gt;st&lt;/sup&gt; application</td>
<td>T-6h</td>
<td>T-4h</td>
</tr>
<tr>
<td>Subject information and consent signed</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening test for blanching response</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history and concomitant diagnosis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination Vital signs</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check of Inclusion / Exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urinary pregnancy test&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<sup>(a)</sup> PR: Pre-Randomisation

<sup>(b)</sup> FU: Follow-Up

<sup>(c)</sup> Urinary pregnancy test: 1st day
<table>
<thead>
<tr>
<th>Day-15 to Day-1</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 16</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Application Phase</td>
<td>PR&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Screening visits</td>
<td>Before 1&lt;sup&gt;st&lt;/sup&gt; application</td>
<td>T-6h</td>
<td>T-4h</td>
</tr>
<tr>
<td>Study Drug Application&lt;sup&gt;2&lt;/sup&gt;</td>
<td>X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Removal of Study Drug (PR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual scoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorimetric measurements</td>
<td>X&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X X X X X X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(1) Female subjects of child bearing potential. Result had to be negative to continue in the study.
(2) According to the randomisation scheme.
(3) Baseline colorimetric measurements were to be performed on all 12 test sites within one hour prior to first drug application (T0 – 6h).
(4) PR: Product Removal
(5) FU: If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit.
Screening visit:
The screening visit was performed within 15 days to 1 day before the first study treatment application (Day 1):
- Subject information and informed consent signed
- Urinary pregnancy test (for female subjects of childbearing potential)
- Test for assessment of the blanching response with the reference product (inclusion criterion no. 2)
- Medical history and concomitant diagnosis
- Concomitant medication
- Physical examination: general aspects, height, weight, cardiovascular and respiratory system, abdomen, lymph nodes, neck including thyroid, skin, neurological examination.
- Vital signs: sitting systolic and diastolic blood pressure (mm Hg) and pulse (beats per minute) after a 5-minute rest
- Inclusion/exclusion criteria checking

On Day 1:
The subjects had to be present at the Centre for about 13 hours. Between each product application/or each pharmacodynamic evaluation, subjects were free to leave the Centre.
- Inclusion/exclusion criteria checking
- Recording of changes in concomitant medication, if any
- Recording of any adverse event occurred since screening visit.
- Allocation of a randomisation number (given in chronological order)
- T0 minus 6-7h: baseline colorimetric measurements were performed on all the test sites (12 sites, 6 per forearm).
- Application period (staggered applications of the tested product according to the randomisation number): from T0 minus 6h to T0 minus 0.25 hour.
- T0: drug removal from all treated sites.
- Pharmacodynamic evaluations on each test site (colorimetric measurements and visual score): T10 min, T2h, T4h, and T6h.

On Day 2:
The subjects had to come back to the Centre on Day 2 in the morning
- Recording of changes in concomitant medication, if any
- Recording of adverse event, if any
- Pharmacodynamic evaluations on each test site (colorimetric measurements and visual score): T19h and T24h.
### 11.7.2 Schedule of Study Procedures – Pivotal Phase

<table>
<thead>
<tr>
<th>Screening Phase</th>
<th>Baseline</th>
<th>Application Phase</th>
<th>PR (PR)</th>
<th>Evaluation Phase</th>
<th>FU (FU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening visits</td>
<td>Before 1st application</td>
<td>D1</td>
<td>ED50</td>
<td>D2</td>
<td>T0</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary pregnancy test (1)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening test for blanching response</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history and concomitant diagnosis</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination and Vital signs</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion criteria</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study drug application (2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Removal of Study Drug</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual scoring</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Colorimetric measurements</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

(1) Female subjects of child bearing potential. Result had to be negative to continue the study.
(2) According to the randomisation scheme.
(3) Baseline colorimetric measurements were to be performed on all 16 test sites within one hour prior to first drug application (T0 – D1).
(4) PR: Product Removal
(5) FU: If an adverse event (serious or non-serious) classified as possibly or probably related to the study treatment or not assessable in relation to the study treatment was ongoing at the last on-treatment visit.

### Screening visit:

The screening visit was performed within 15 days to 1 day before the first study treatment application (Day 1)
- Subject information and informed consent signed
- Urinary pregnancy test (for female subjects of childbearing potential)
- Test for assessment of the blanching response with the reference product (inclusion criterion no. 2)
- Medical history and concomitant diagnosis
- Concomitant medication
- Physical examination general aspects, height, weight, cardiovascular and respiratory system, abdomen, lymph nodes, neck including thyroid, skin, neurological examination.
- Vital signs: sitting systolic and diastolic blood pressure (mm Hg) and pulse (beats per minute) after a 5-minute rest
- Inclusion/exclusion criteria checking

**On Day 1:**
The subjects had to be present at the Centre for about 13 hours. Between each product application / or each pharmacodynamic evaluation, subjects will be free to leave the Centre.
- Inclusion/exclusion criteria checking
- Recording of changes in concomitant medication, if any
- Recording of any adverse event that had occurred since screening visit.
- Allocation of a randomisation number (given in chronological order)
- T0 minus D2 baseline colorimetric measurements will be performed on all the test sites (16 sites, 8 per forearm).
- Application period (staggered applications of the tested product according to the randomisation number): from T0 minus D2 to T0 minus D1 hour
- Application times:
  - T0 minus D1
  - T0 minus ED50
  - T0 minus D2
- T0: drug removal from all treated sites.
- Pharmacodynamic evaluations on each test site (colorimetric measurements and visual score): T10 min, T2h, T4h, and T6h.

**On Day 2:**
The subjects had to come back at the Centre on Day 2 in the morning
- Recording of changes in concomitant medication, if any
- Recording of adverse event, if any
- Pharmacodynamic evaluations on each test site (colorimetric measurements and visual score): T19h and T24h.

11.7.3 Evaluation criteria

11.7.3.1 Pharmacodynamic assessments
The conditions for pharmacodynamic assessments (room temperature at below 24.9°C and standard light) had to be identical at each evaluation time.
Global view of pharmacodynamic assessment

The pilot and the pivotal phases of the study followed exactly the same schedule of evaluations. For both phases of the study, skin blanching effect assessment were performed both subjectively using a 5-point (0-4) visual assessment scale and objectively with the Minolta CR 300 Chromometer over a 24 h period as described in the figure below.

Visual score and colorimetric measurements for the Pilot and the Pivotal Phases of the Study

Assessment times were 10 minutes, 2, 4, 6, 19 and 24 hours after pro-duct removal (T0).

11.7.3.2 Primary criterion

For both the pilot and the pivotal phases, the primary criterion was the colorimetric measurement $a^*$. The $L^* a^* b^*$ system recommended by the CIE (Commission Internationale de l’Eclairage 1976) was used for the objective evaluation of the skin color. At each time, two successive series of measurements were performed on each test site. The primary efficacy variable was the $a^*$ value.
**Schedule**

The colorimetric measurements on each test site were performed at the following times:
- **On Day 1:** before T0 minus 6h (= baseline evaluation within one hour prior to the first drug application), T10 min, T2h, T4h and T6h after drug removal.
- **On Day 2:** T19h and T24h after drug removal.

### 11.7.3.3 Colorimetric Evaluation Method

For both the pilot and the pivotal phases, the colorimetric measurements were performed with a CR 300 Chromameter (Minolta).

The Minolta CR 300 Chromameter is a portable instrument with a flexible hand-held probe which can be moved very easily from one site to another. The measured area is 8 mm in diameter. This reflected light colorimeter offers five different color systems for measuring absolute chromaticity. The L* a* b* system is recommended by the CIE.

Color is expressed in a three dimensional space. The L* value (luminance) gives the relative brightness ranging from total black (L*=0) to total white (L*=100). The a* value represents the balance between the red (positive values) and the green (negative values). The b* value represents the balance between the yellow (positive values) and the blue (negative values). The skin blanching effect leads to an increase of the L* value and a decrease of the a* value compared to baseline. The b* value is not modified by the blanching phenomena and will not be taken into account for the study analysis (b* reflects mainly pigmentation changes rather than vascular changes).

Before use, the calibration channel of the colorimeter was brought to standard white plate level (calibration plate CR-A). Proper calibration was performed each time the instrument was turned on.

### 11.7.3.4 Secondary criterion

For both the pilot and the pivotal phases, the secondary criterion was the visual score.

**Schedule**

Visual scorings on each test site were performed independently by two trained blinded evaluators at the following times:
- **On Day 1:** T10 min, T2h, T4h and T6h after drug removal.
- **On Day 2:** T19h and T24h after drug removal.
Note: At the screening visit (Day-15 to Day-1), an assessment of the blanching response (screening of responder subjects) was carried out by the visual scoring (no colorimetric measurement). The test was performed on one site not located on the forearms. The visual skin blanching assessment was performed by a single trained evaluator according to the same method as described below in 11.7.3.5. A subject was considered to have a responder status if he/she showed a visual reading of at least one unit.

11.7.3.5 Visual Scoring Evaluation Method
Visual assessment of blanching was made subjectively and individually by the two trained evaluators, according to the following score:

- 0 = no change in skin color
- 1 = slight (barely visible) blanching
- 2 = obvious blanching
- 3 = intense blanching
- 4 = blanching judged to be maximal

Intermediate scores (half units) were used when needed (e.g., 0.5 for a doubtful blanching). At each evaluation time, 2 visual score values (one per trained evaluator) were recorded for each test site.

11.7.3.6 Safety assessments

General safety
For both the pilot and the pivotal phases, the adverse events were recorded spontaneously during the study on an ongoing manner and recorded in the subject’s medical record and in the CRF.

Local tolerance assessment
Local tolerance on the test sites were assessed by the investigator during the entire study. In case signs of irritation, this was recorded in the medical dossier and on the Adverse Event Form in the CRF.

11.7.3.7 Local Analysis
A urine pregnancy test was performed at the investigative centre at baseline in female subjects of child bearing potential. The test kits were provided by LEO.
11.7.4 Adverse Events

*Adverse Event (AE)*: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

*Adverse Drug Reaction (ADR)*: in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

At all visits after treatment start, the subject was asked a non-leading question by the investigator: “Since I last saw you, have you had any problems?”

No specific symptoms were asked for.

If the answer was “NO”, no further questions were asked. If the answer was “YES”, the investigator recorded the event’s nature, intensity, duration, location for cutaneous adverse events, suspected causal relationship to the investigational product and outcome.

It was important that the investigator also observed the subject for any changes not reported by the subject, and recorded these changes.

Only medically qualified (sub)investigators could assess the subject for (Serious) Adverse Events.
11.7.4.1 Reporting of Adverse Events

Events, either reported by the subject or observed by the investigator, that fall into any of the above definitions were to be recorded on the adverse event page of the CRF book and described in the following manner:

The NATURE of the event was to be described in precise, standard medical terminology (i.e., not necessarily the exact words used by the patient). If known, a specific diagnosis should be stated (e.g., allergic contact dermatitis).

The INTENSITY of the event was described in terms of mild, moderate or severe according to the investigator’s clinical judgement.

Mild. The adverse event does not interfere in a significant manner with the patient’s normal functioning level. It may be an annoyance.

Moderate. The adverse event produces some impairment of functioning but is not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe. The adverse event produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient.

The DURATION of the event was described by the start date and end date.

The LOCATION for cutaneous adverse events was described in terms of location on a test site or distant from the test sites.

The CAUSAL RELATIONSHIP of the event 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.

Probable
Follows a reasonable temporal sequence from administration of the investigational product.

Could not be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.
Follows a known pattern of response to the investigational product.

Disappears or decreases on cessation or reduction in dose of the investigational product.

Reappears or worsens upon rechallenge.

**Possible**
Follows a reasonable temporal sequence from administration of the investigational product.

Could be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.

Follows a known pattern of response to the investigational product.

**Not related**
Does not follow a reasonable temporal sequence from administration of the investigational product.

Could be reasonably explained by the subject’s clinical state, environmental or toxic factors or other therapies administered to the subject.

Does not reappear or worsen upon rechallenge.

Does not follow a known pattern of response to the investigational product.

**Not assessable**
The adverse event cannot yet be judged otherwise because present information is insufficient or contradictory. A final judgement (i.e., probably, possibly, or not related) shall be made as more information becomes available at the latest when the subject has completed the trial.

The **OUTCOME** of the event was described in terms of:

- Recovered/resolved
- Recovering/resolving

“(S)AE stop date” should be provided
Can be used in cases where patient is known to
be clearly recovering from an event. Event is, however, not resolved yet. Follow-up required

Not recovered/not resolved  
Event is ongoing  
Follow-up required

Recovered with sequelae/ 
resolved with sequelae  
Used only with persistent incapacity/life long sequelae, e.g., like blindness after diabetes mellitus, hemiparesis after stroke  
“(S)AE stop date” should be provided

Fatal  
“(S)AE stop date” (date of death) should be provided only for the events leading to death

Unknown  
Unknown to Investigator, e.g., subject lost to follow-up

If the outcome was “not recovered/not resolved” or “recovering/resolving” or “unknown” the AE stop date was to be left blank.

If the outcome was “recovered/resolved” or “recovered with sequelae/resolved with sequelae” or “fatal” the AE stop date was to be entered.

During the trial all serious and non-Serious Adverse Events were to be followed up to determine the final outcome.

Once a healthy subject had completed the trial, the investigator was to follow-up for outcome on all non-Serious Adverse Events classified as possibly/probably related to investigational product or not assessable for two weeks or until final outcome was determined, whichever came first.

**Pregnancy**

Pregnancy which occurred during a clinical trial with an investigational product was to be reported to LEO by use of the LEO Serious Adverse Event (SAE) Form – Clinical Trial and handled as an SAE with regard to reporting time frame. All pregnancies were to be followed-up until conclusion.
11.7.5 Serious Adverse Events

11.7.5.1 Definition of Serious Adverse Events

**Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR):** Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect

or other medically important conditions

\(^a\)

\(^a\) Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (See the ICH Guideline E2A)

11.7.5.2 Reporting of Serious Adverse Events

Any serious adverse event related or unrelated to the investigational product occurring during the course of the trial were to be reported to LEO within **ONE** working day after first knowledge by the investigator.

Any Serious Adverse Event, related or unrelated to any trial procedures (e.g., wash-out, biopsies) occurring after informed consent had been obtained, and until the subject’s completion of the trial, were to be reported to LEO within **ONE** working day after first knowledge by the investigator.

**Note:** Hospitalisation or prolonged hospitalisation for logistic/convenience reasons or hospitalisation solely for study-related purposes do not fulfil the criteria for being an untoward medical occurrence and are therefore not a Serious Adverse Event.

The completed LEO Serious Adverse Event (SAE) Form – Clinical Trial was to be sent/faxed to the local LEO company.
Reports were made using the **SERIOUS ADVERSE EVENT (SAE) FORM - CLINICAL TRIAL**, supplied by LEO. The information provided on the form included a description of the clinical course of the serious adverse event and an assessment of the intensity, causal relationship to the investigational product(s) and/or trial procedures, the action taken and the outcome to date.

The initial report was followed by a detailed description later which might include copies of hospital records, autopsy reports and other documents when requested and applicable.

If an investigator was in doubt whether to regard an adverse event as serious or not, the event was serious until the opposite had been established.

The Independent Ethics Committee(s) and National Health Authorities were to be notified on such an event in writing according to local requirements.

All serious adverse event descriptions were also recorded on the adverse event page of the CRF book in addition to being reported on the LEO Serious Adverse Event (SAE) Form - Clinical Trial.

For all serious adverse events classified as possibly/probably related to Investigational product or not assessable (including those ongoing at the time the subject completed the trial and those serious adverse events coming to the investigator’s awareness within 2 weeks follow-up period) the investigator followed-up for final outcome and all queries had been resolved. Details of follow-up have been given (e.g., discontinuation of investigational treatment, if specific treatment was required, if hospitalisation was required etc.).

**11.7.6 Changes to Planned Study Procedures**

Not applicable.

**11.8 STATISTICAL ANALYSIS**

**11.8.1 Planned Analysis**

The statistical analysis is described in the protocol and further specified in the statistical analysis plan (SAP), see Appendix III. The following is a brief summary. For a more detailed description, see the statistical appendix, Appendix IV.
11.8.1.1 Handling of missing data

Methods for handling any missing values were evaluated at the blind review of the data and were described in the statistical analysis plan, Appendix III.

11.8.1.2 Baseline characteristics

Continuous demographic variables (age, weight and height) were summarised, using mean, standard deviation, minimum, maximum and number of available observations. Qualitative demographic characteristics were summarised by counts and percents. Other subject characteristics (anomalies in physical examination, prior medication, inclusion / exclusion checklist) were only listed.

11.8.1.3 Sample size

Twelve subjects is the number recommended by the FDA guideline for the pilot phase. Based on the results from the pilot phase, it was estimated that (see Section 14.4.1) approximately 90 subjects were to be enrolled in the pivotal phase in order to have 40 to 60 evaluable subjects i.e., subjects who meet both the “responder” and the “detector” criteria defined in the FDA guideline.

11.8.1.4 Protocol deviations

Decisions regarding exclusion of subjects and/or subject data from the statistical analyses were documented before locking and unblinding of the database.

11.8.1.5 Data sets analysed

All subjects included in the study (i.e., informed consent signed and a CRF book started) were accounted for in the study report. All randomised subjects who received the study drug and provided information on safety constituted the safety analysis set, and were analysed for safety. Randomised subjects who received study drug, who provided post-randomisation data, who attended all the study visits, who fulfilled all the inclusion criteria and who did not meet any of the exclusion criteria at enrolment or during the study constituted the per protocol analysis set and were analysed for pharmacodynamics.

The per protocol analysis set for the pivotal phase was further defined by the following:

1) Only the data of detectors i.e. individual subjects whose AUEC_{0-24h} values at D_1 and D_2 were both negative and meeting the dose duration-response criterion below, were included in the data analysis. The dose duration criterion was:
where AUEC₀₋₂₄h at D₂ and AUEC₀₋₂₄h at D₁ was the mean of the computed left and right arm values.

2) Only the subjects with a complete data set were included in the data analysis.

Pharmacodynamic analysis was done on the per protocol analysis set. Safety parameters were evaluated on the safety analysis set.

11.8.1.6 Pharmacodynamic analysis

11.8.1.6.1 Primary response criterion

Pilot Phase
The primary criterion was the colorimetric parameter a*. The mean of two successive measurements performed on each test site was used. The variable subjected to analysis was denoted Δa* and was computed by first subtracting the baseline values – i.e. the a* values immediately after removal of the application. Then, in this new data set, the mean values at the untreated control sites were subtracted separately for each arm. The area under the effect curve from 0 to 24 hours (AUEC₀₋₂₄h) for Δa* (baseline adjusted and untreated control site-corrected values) was calculated by the trapezoidal method for each individual test site. In the computation, theoretical, not actual, time points were used.

The dose duration-response data were analysed using a non-linear least square regression to determine the population ED₅₀ value which served as the approximate dose duration for the bioequivalence comparison in the pivotal study. In accordance with the FDA guideline (10) the D₁ and D₂ were also estimated.

Pivotal Phase
The primary criterion was the colorimetric parameter a*. The mean of two successive measurements performed on each test site was used. The variable subjected to analysis was denoted Δa* and was computed by first subtracting the baseline values – i.e. the a* values immediately after removal of the application. Then, in this new data set, the mean values at the untreated control sites were subtracted separately for each arm. The area under the effect curve from 0 to 24 hours (AUEC₀₋₂₄h) for Δa* (baseline adjusted and untreated control site-corrected values) was calculated by the trapezoidal method for each individual test site. In the computation, theoretical, not actual, time points were used.
11.8.1.6.2 Bioequivalence

Bioequivalence was estimated using Locke’s method for calculating the 90% confidence interval for the ratio of average AUEC0-24h (test product/reference) \(^{(10)}\).

11.8.1.6.3 Secondary response criteria

Pilot Phase

For the visual blanching score, analysed variables were the mean of the visual blanching scores (from 0 to 4) between the two evaluators, for each time.

The dose duration-response data were fitted. The ED50, D1 and D2 were estimated.

Pivotal Phase

For the visual blanching score, the analysed variable was the mean of the visual blanching scores (from 0 to 4) between the two readers, for each time.

11.8.1.7 Analysis of Safety

11.8.1.7.1 Adverse events

The safety evaluation was based upon the review of the individual values and descriptive statistics (summary tables, graphics).

All the adverse events recorded during the study were coded according to version 6.1 of the Medical Dictionary for Regulatory Activities (MedDRA). They were listed by subject including time of onset, time from the first administration of study drug, duration, intensity, action taken, corrective therapies, outcome, relationship to study drug and seriousness.

A treatment emergent adverse event was an adverse event occurring after the first dose of trial drug has been applied at the screening test for blanching response. The treatment emergent adverse events were to be summarised by tabulating:

- The number of subjects experiencing each type of adverse event (according to MedDRA preferred term).
- Adverse drug reactions, i.e. adverse events where the investigator had not excluded a causal relationship to study medication (not described relationship as “not related”) were evaluated separately.
- The causal relationship of adverse events to study medication and the intensity of adverse drug reactions by treatment group. Where there were several recordings of casual relationship and intensity for the same event, casual relationship were taken from the last report of the
event (since that is when the investigator was in possession of most information and so best able to judge casual relationship) and intensity was taken as the worst ever recording
- Serious adverse events were evaluated separately.

Due to the low number of events, no safety tables were made. These data were instead described in the text and listed.

11.8.1.7.2 Concomitant treatments
The concomitant medications were coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification. They were summarised by tabulating the number and percent of subjects having received each medication belonging to each therapeutic class.

11.8.2 Changes in the Conduct of the Study or Planned Analyses
No changes in the conduct of the study or planned analyses were made.

11.9 DATA MONITORING COMMITTEES
Not applicable.

11.10 QUALITY ASSURANCE/AUDIT
LEO has implemented a system of quality assurance, including all the elements described in this report. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical studies are conducted in compliance with regulatory requirements and Good Clinical Practice. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Investigational sites, facilities, and all data (including sources) and documentation were available for GCP audit by LEO or inspection by competent authorities.

No audits were conducted for this trial.

11.11 DATA HANDLING
LEO, as Sponsor of this study, is responsible to the Authorities for assuring the proper conduct of the trial with regard to protocol adherence and validity of the data recorded on the Case Report Forms. Monitors were assigned to serve as the principal link between (sub)investigators and LEO and to advise the investigators in the collection and maintenance of complete, legible, well organised, and easily retrievable data for the trial. In addition, they
were to explain any aspect of the (conduct of the) trial, including interpretation of the protocol, and purpose of collection of the specified data and reporting responsibilities to the investigators.

Data recorded on the CRFs were entered into the LEO database as soon as possible after receipt and verification of the data by LEO had taken place.

The computerisation of the data in the CRFs was done as two independent data entries which were compared and reconciled to eliminate key stroke errors.

Systematic data validation was performed by LEO data managers and the study statistician to obtain a clean database prior to the statistical analysis.

Data were and are handled in accordance with the general terms and conditions of the authorisation from the Danish Data Protection Agency to LEO Pharma A/S, as required, according to the Danish Personal Act and any national legislation implementing the Data Protection Directive (95/46/EC).

LEO DK is considered data responsible for all international clinical trials sponsored by LEO.

12 STUDY PERIOD

12.1 STUDY DATES

Pilot Phase
Date of enrolment of first subject: 07 March 2005
Date of enrolment of last subject: 10 March 2005
Date of completion of last subject: 18 March 2005

Pivotal Phase
Date of enrolment of first subject: 02 May 2005
Date of enrolment of last subject: 14 June 2005
Date of completion of last subject: 17 June 2005

12.2 UNBLINING OF THE STUDY

Pilot Phase
The database was locked on 15 April 2005 following validation of the blinded data.
The randomisation schedule was released from the R&D, QA Department on 15 April 2005.

**Pivotal Phase**
The database was locked on 23 August 2005 following validation of the blinded data.
The randomisation schedule was released from the R&D, QA Department on 23 August 2005.

### 13 STUDY POPULATION

#### 13.1 DISPOSITION OF STUDY SUBJECTS

**Pilot Phase**
Eighteen subjects were enrolled, of which 6 (CRF=thestrip) were withdrawn since they were ‘non-responders’. (See Section 11.4.1 for a definition of responder). Since no others were withdrawn, 12 subjects were randomised.

The number of subjects who attended each visit and the analysis sets is illustrated in Figure 1.

Figure 1: Visit attendance and subject analysis sets, pilot phase

<table>
<thead>
<tr>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended screening visit = 18</td>
</tr>
<tr>
<td>Enrolled subjects =</td>
</tr>
<tr>
<td>6 subjects (CRF=thestrip) were ‘non responders’ (inclusion criterion 3)</td>
</tr>
<tr>
<td>Attended visit 1 = Randomised subjects = 12</td>
</tr>
<tr>
<td>Safety Analysis Set =</td>
</tr>
<tr>
<td>Per Protocol Analysis Set =</td>
</tr>
<tr>
<td>Attended visit 2 = 12</td>
</tr>
</tbody>
</table>
Pivotal Phase

Ninety-five subjects were enrolled, of which 25 were withdrawn, due to reasons specified in Table 1. Hence 70 subjects were randomised.

Table 1: Reasons for non-randomisation, pivotal phase

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject was a non-responder</td>
<td>24</td>
</tr>
<tr>
<td>Subject was late</td>
<td>1</td>
</tr>
</tbody>
</table>

The process of enrolment is illustrated in Figure 2 and Figure 3. In the latter figure, also the analysis sets are depicted.

Figure 2: Subject recruitment: enrolled subjects, pivotal phase
Figure 3: Visit attendance and schematic presentation of the analysis sets, pivotal phase

Number of subjects

- Attended screening visit = Enrolled subjects = 95
- 24 'non-responders' (inclusion criterion 3)
- 1 'other reasons' (the subject was late for visit 1)

Attend visit 1 = Randomised subjects = Safety Analysis Set = 70

Attend visit 2 = 70

Per Protocol Analysis Set = 27

43 were 'non-detectors'

13.2 PROTOCOL DEVIATIONS

In the pilot study, in the randomisation scheme provided by the Sponsor, there was an inversion of the forearms when compared to the study protocol.

Sites 1 to 6 were indicated as localised on left forearms and sites 7 to 12 were indicated as localised on right forearms. For the applications, the investigation team only considered the site numbers so that:

- Sites 1 to 6 were applied on right forearms,
- Sites 7 to 12 were applied on left forearms, as indicated in the protocol.

An error in the randomisation order occurred on 26 May 2005.
The subject who should have received applications according to the randomisation for subject number received by error the randomisation for subject number. The following subjects randomised on the same day received treatments according to the randomisation for subject numbers

With the Sponsor's agreement, randomisation number and were therefore later assigned to the first subjects of the following group.

These deviations were considered as minor deviations without impact on the study results.

14 EFFICACY EVALUATION

14.1 DATA SETS ANALYSED

14.1.1 Full Analysis Set

Pilot Phase
In accordance with the protocol, no full analysis set (Intention-To-Treat analysis set) was defined, as the analysis of pharmacodynamics was only performed for the per protocol analysis set.

Pivotal Phase
In accordance with the protocol, no full analysis set (Intention-To-Treat analysis set) was defined, as the analysis of pharmacodynamics will only be performed for the per protocol analysis set.

14.1.2 Safety Analysis Set

Pilot Phase
All 12 randomised subjects received study medication and provided information on safety following start of treatment. The safety analysis set therefore consists of 12 subjects.

This set of subjects was used for all safety analyses.

Pivotal Phase
All 70 randomised subjects received study medication and provided information on safety following start of treatment. The safety analysis set therefore consists of 70 subjects.

This set of subjects was used for all safety analyses.
14.1.3 Per-Protocol Analysis Set

Pilot Phase
The 12 randomised subjects all received study medication, provided pharmacodynamic data following randomisation, attended both study visits, fulfilled all inclusion criteria and did not meet any of the exclusion criteria at enrolment or during the study. The per-protocol analysis therefore consists of 12 subjects.

Pivotal Phase
All 70 randomised subjects received study medication, provided pharmacodynamic data following randomisation, attended both study visits, fulfilled all inclusion criteria, and did not meet any of the exclusion criteria at enrolment or during the study.

Only the data of detectors was included in the per protocol analysis set – i.e. individual subjects whose AUEC_{0-24h} values at D_1 and D_2 were both negative and who met the dose duration criterion: The ratio between AUEC_{0-24h} at D_2 and AUEC_{0-24h} at D_1 is at least 1.25, where AUEC_{0-24h} and D_1 and D_2 is the mean of the computed left and right arm values. Whether subjects were detectors was determined after unblinding, since the locations for dose durations D_1 and D_2 were only known after unblinding of treatment allocation. In total, 43 subjects were found to be non-detectors. The CRF numbers of the non-detectors are listed in listing 7, pivotal part, Appendix XI. All subjects had a complete set of data for a*. Furthermore, all dose duration applications were performed as expected (i.e. there were no deviations from the theoretical time intervals).

The per protocol analysis set therefore consists of 27 subjects: 70 minus the 43 non-detectors (as determined after unblinding according to the dose duration criterion above).

14.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Pilot phase
The age, sex, skin type according to the Fitzpatrick scale (11), weight and height of each subject were recorded and accounted for in Table 2 to Table 6 using standard summary statistics.
Table 2: Age: Randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All randomised subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>30.9</td>
</tr>
<tr>
<td>Std</td>
<td>5.9</td>
</tr>
<tr>
<td>Min</td>
<td>23</td>
</tr>
<tr>
<td>Max</td>
<td>40</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 3: Sex: Randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Sex</th>
<th>All randomised subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Females</td>
<td>8</td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 4: Skin type: Randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Skin type</th>
<th>All randomised subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of subjects</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>10</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 5: Weight: Randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>All randomised subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>68.1</td>
</tr>
<tr>
<td>Std</td>
<td>15.1</td>
</tr>
<tr>
<td>Min</td>
<td>49</td>
</tr>
<tr>
<td>Max</td>
<td>100</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 6: Height: Randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>All randomised subjects (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>167.8</td>
</tr>
<tr>
<td>Std</td>
<td>6.6</td>
</tr>
<tr>
<td>Min</td>
<td>156</td>
</tr>
<tr>
<td>Max</td>
<td>178</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
</tr>
</tbody>
</table>
Table 7 contains the a* values at baseline for all 9 dose durations.

Table 7: Chromometer a*: randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Dose duration (h)</th>
<th>0</th>
<th>0.25</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.08</td>
<td>9.20</td>
<td>9.38</td>
<td>8.99</td>
<td>9.09</td>
</tr>
<tr>
<td>Std</td>
<td>1.03</td>
<td>1.45</td>
<td>1.23</td>
<td>1.27</td>
<td>1.26</td>
</tr>
<tr>
<td>Min</td>
<td>6.56</td>
<td>7.27</td>
<td>6.73</td>
<td>7.11</td>
<td>6.96</td>
</tr>
<tr>
<td>Max</td>
<td>11.51</td>
<td>11.87</td>
<td>11.95</td>
<td>11.35</td>
<td>11.77</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

(Continued)

<table>
<thead>
<tr>
<th>Dose duration (h)</th>
<th>1.5</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.47</td>
<td>9.01</td>
<td>9.03</td>
<td>9.06</td>
</tr>
<tr>
<td>Std</td>
<td>1.14</td>
<td>1.12</td>
<td>1.26</td>
<td>1.07</td>
</tr>
<tr>
<td>Min</td>
<td>7.01</td>
<td>6.88</td>
<td>7.46</td>
<td>7.32</td>
</tr>
<tr>
<td>Max</td>
<td>10.99</td>
<td>10.87</td>
<td>11.60</td>
<td>10.81</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>
Concurrent diagnoses are summarised in Table 8, and concomitant medication in Table 9.

Table 8: Number of subjects with concurrent diagnoses at baseline classified by MedDRA Primary System Organ Class: randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>System Organ Classification 1)</th>
<th>All randomised subjects (n=12)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of diagnoses</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>

Total number of diagnoses 2) 32
Total number of subjects 12 100.0

1) Classification according to MedDRA version 6.1
2) Different Diagnoses within the same preferred term and involving the same subject have been counted as one. A single subject could appear in multiple classes

Table 9: Concomitant medication at baseline: randomised subjects, pilot phase

<table>
<thead>
<tr>
<th>Anatomical Therapeutic Chemical (ATC) classification index Level 1</th>
<th>All randomised subjects (n=12)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of drugs</td>
<td>Number of subjects</td>
</tr>
<tr>
<td>Genito urinary system and sex hormones</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Systemic hormonal prep, excl sex horm. and insulins</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Total number of drugs taken 1) 7
Total number of subjects 6 50.0

1) Drugs with the same ATC classification level 4 code and generic name/preferred name which have been taken by the same subject have been counted as one
Pivotal phase

The age, sex, skin type according to the Fitzpatrick scale (11), weight and height of each subject were recorded and accounted for in Table 10 to Table 14 using standard summary statistics.

Table 10: Age: Randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>28.0</td>
</tr>
<tr>
<td>Std</td>
<td>5.7</td>
</tr>
<tr>
<td>Min</td>
<td>19</td>
</tr>
<tr>
<td>Max</td>
<td>41</td>
</tr>
<tr>
<td>N</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 11: Sex: Randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Sex</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>Females</td>
<td>58</td>
</tr>
<tr>
<td>Males</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 12: Skin type: Randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Skin type</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>58</td>
</tr>
<tr>
<td>IV</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 13: Weight: Randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>61.1</td>
</tr>
<tr>
<td>Std</td>
<td>11.1</td>
</tr>
<tr>
<td>Min</td>
<td>43</td>
</tr>
<tr>
<td>Max</td>
<td>95</td>
</tr>
<tr>
<td>N</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 14: Height: Randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>167.7</td>
</tr>
<tr>
<td>Std</td>
<td>9.9</td>
</tr>
<tr>
<td>Min</td>
<td>150</td>
</tr>
<tr>
<td>Max</td>
<td>203</td>
</tr>
<tr>
<td>N</td>
<td>70</td>
</tr>
</tbody>
</table>
Table 15 contains the $a^*$ values at baseline, divided into five groups according to the type of application, where also the untreated control sites are included.

**Table 15: Chromometer $a^*$: randomised subjects, pivotal phase**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DAIVOBET/DOVOBET</th>
<th>DIPROSONE ointment</th>
<th>DIPROSONE ointment</th>
<th>DIPROSONE ointment</th>
<th>DIPROSONE ointment</th>
<th>Untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>EdS0</td>
<td>EdS0</td>
<td>D1</td>
<td>D2</td>
<td>Untreated</td>
</tr>
<tr>
<td>BASELINE</td>
<td>Mean</td>
<td>8.44</td>
<td>8.56</td>
<td>8.60</td>
<td>8.55</td>
<td>8.49</td>
</tr>
<tr>
<td></td>
<td>Std</td>
<td>1.53</td>
<td>1.55</td>
<td>1.62</td>
<td>1.54</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>4.81</td>
<td>4.67</td>
<td>5.12</td>
<td>4.96</td>
<td>4.85</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>13.48</td>
<td>13.30</td>
<td>15.62</td>
<td>12.61</td>
<td>13.45</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>280</td>
<td>280</td>
<td>140</td>
<td>140</td>
<td>280</td>
</tr>
</tbody>
</table>
Concurrent diagnoses are summarised in Table 16, and concomitant medication in Table 17. More detailed information is given in listing 9, pivotal part, Appendix XI.

Table 16: Number of subjects with concurrent diagnoses at baseline by MedDRA Primary System Organ Class: randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>System Organ Classification</th>
<th>Number of diagnoses</th>
<th>Number of subjects</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital, familial and genetic disorders</td>
<td>2</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>2</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>5</td>
<td>5</td>
<td>7.1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>15</td>
<td>13</td>
<td>18.6</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>4</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>21</td>
<td>18</td>
<td>25.7</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>12</td>
<td>11</td>
<td>15.7</td>
</tr>
<tr>
<td>Investigations</td>
<td>3</td>
<td>3</td>
<td>4.3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>4</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>4</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>13</td>
<td>13</td>
<td>18.6</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>1</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>4</td>
<td>4</td>
<td>5.7</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>20</td>
<td>15</td>
<td>21.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>32</td>
<td>29</td>
<td>41.4</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>92</td>
<td>53</td>
<td>75.7</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>3</td>
<td>3</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Total number of diagnoses: 240
Total number of subjects: 69

1) Classification according to MedDRA version 6.1
2) Different Diagnoses within the same preferred term and involving the same subject have been counted as one. A single subject could appear in multiple classes.
Table 17: Concomitant medication at baseline: randomised subjects, pivotal phase

<table>
<thead>
<tr>
<th>Anatomical Therapeutic Chemical (ATC) classification index Level 1</th>
<th>All randomised subjects (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of drugs</td>
</tr>
<tr>
<td>Genito urinary system and sex hormones</td>
<td>44</td>
</tr>
<tr>
<td>Systemic hormonal prep., excl. sex horm. and insulins</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td><strong>Total number of drugs taken</strong></td>
</tr>
<tr>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>

1) Drugs with the same ATC classification level 4 code and generic name/preferred name which have been taken by the same subject have been counted as one.

14.3 TREATMENT

14.3.1 Use of and Compliance with Prescribed Trial Medication

Pilot Phase
For all 12 randomised subjects the trial medication was applied as prescribed, i.e. 100% of the subjects were fully compliant.

Pivotal Phase
For all 70 randomised subjects the trial medication was applied as prescribed, i.e. 100% of the subjects were fully compliant.

14.4 PHARMACODYNAMIC RESULTS

14.4.1 Primary Response Criterion

Pilot Phase
The primary criterion was the colorimetric parameter \( a^* \). The mean of two successive measurements performed on each test site was used. The variable subjected to analysis was denoted \( \Delta a^* \) and was computed by first subtracting the baseline values – i.e. the \( a^* \) values recorded immediately after removal of the application. Then, in this new data set, the mean values at the untreated control sites were subtracted separately for each arm. See Table 18, Table 19 and Figure 4. The other colorimetric parameters \( L^* \) and \( b^* \) were only listed. The area under the effect curve from 0 to 24 hours (AUEC\textsubscript{0-24h}) for \( \Delta a^* \) (baseline adjusted and untreated control site-corrected values) was calculated by the trapezoidal method for each...
individual test site. In the computation, theoretical, not actual, time points were used. See Table 20 and Figure 5.

Figure 4: Mean chromometer $a^*$ adjusted for baseline per dose duration by measurement time: per protocol analysis set, pilot phase.
Figure 5: Mean AUEC<sub>0-24h</sub> for Δ<sup>a</sup>* (baseline and untreated control site corrected) by dose duration: per protocol analysis set, pilot phase.
Table 18: Mean a* by treatment and assessment time: per protocol analysis set, pilot phase

<table>
<thead>
<tr>
<th>Time after removal (h)</th>
<th>0</th>
<th>0.25</th>
<th>0.5</th>
<th>0.75</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>4</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Std</td>
<td>1.03</td>
<td>1.45</td>
<td>1.23</td>
<td>1.27</td>
<td>1.26</td>
<td>1.14</td>
<td>1.12</td>
<td>1.26</td>
<td>1.07</td>
</tr>
<tr>
<td>Min</td>
<td>6.56</td>
<td>7.27</td>
<td>6.73</td>
<td>7.11</td>
<td>6.96</td>
<td>7.01</td>
<td>6.88</td>
<td>7.46</td>
<td>7.32</td>
</tr>
<tr>
<td>Max</td>
<td>11.51</td>
<td>11.87</td>
<td>11.95</td>
<td>11.35</td>
<td>11.77</td>
<td>10.99</td>
<td>10.87</td>
<td>11.60</td>
<td>10.81</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>T10MIN</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.25</td>
<td>9.24</td>
<td>9.43</td>
<td>9.11</td>
<td>8.65</td>
<td>8.96</td>
<td>8.94</td>
<td>8.57</td>
<td>8.08</td>
</tr>
<tr>
<td>Std</td>
<td>1.17</td>
<td>1.33</td>
<td>1.23</td>
<td>1.36</td>
<td>1.01</td>
<td>1.26</td>
<td>1.23</td>
<td>1.42</td>
<td>1.37</td>
</tr>
<tr>
<td>Min</td>
<td>6.35</td>
<td>7.32</td>
<td>6.54</td>
<td>6.79</td>
<td>6.54</td>
<td>5.99</td>
<td>6.94</td>
<td>6.31</td>
<td>5.97</td>
</tr>
<tr>
<td>N</td>
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<td>12</td>
<td>12</td>
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<tr>
<td><strong>T2H</strong></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>9.16</td>
<td>9.08</td>
<td>8.96</td>
<td>8.90</td>
<td>8.70</td>
<td>9.07</td>
<td>8.68</td>
<td>8.19</td>
<td>7.75</td>
</tr>
<tr>
<td>Std</td>
<td>1.07</td>
<td>1.83</td>
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<td>1.28</td>
<td>1.31</td>
<td>1.11</td>
<td>1.26</td>
<td>1.66</td>
<td>1.52</td>
</tr>
<tr>
<td>Min</td>
<td>6.74</td>
<td>5.87</td>
<td>6.31</td>
<td>6.57</td>
<td>6.31</td>
<td>7.08</td>
<td>6.86</td>
<td>6.09</td>
<td>4.56</td>
</tr>
<tr>
<td>Max</td>
<td>11.73</td>
<td>12.79</td>
<td>10.93</td>
<td>11.17</td>
<td>11.82</td>
<td>11.54</td>
<td>11.80</td>
<td>12.38</td>
<td>9.89</td>
</tr>
<tr>
<td>N</td>
<td>48</td>
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<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
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<td><strong>T4H</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>9.24</td>
<td>8.99</td>
<td>8.88</td>
<td>8.79</td>
<td>8.83</td>
<td>8.68</td>
<td>8.20</td>
<td>7.85</td>
<td>7.77</td>
</tr>
<tr>
<td>Std</td>
<td>0.95</td>
<td>1.49</td>
<td>1.29</td>
<td>1.36</td>
<td>1.13</td>
<td>1.06</td>
<td>1.14</td>
<td>1.27</td>
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Table 19: Mean Δa* (baseline adjusted and untreated control site corrected) by treatment and assessment time: per protocol analysis set, pilot phase

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In Table 20 the mean area under the effect curve is tabulated by treatment.

Table 20: Mean AUEC_{0-24h} for Δa* (baseline adjusted and untreated control site corrected) by treatment: per protocol analysis set, pilot phase

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Table 21 contains the estimates of $D_1$, $D_2$ and $ED_{50}$. See the statistical appendix, Appendix IV.

Table 21: Parameter estimates from Emax model fitted by nonlinear least squares regression, pilot phase

<table>
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<tr>
<th>$E_{max}$</th>
<th>$ED_{50}$ (h)</th>
<th>$D_1$ (h)</th>
<th>$D_2$ (h)</th>
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However, for practical reasons, the values that were actually used were: $ED_{50}=20$ min (0.33h), $D_1=5$ min (0.08h), $D_2=60$ min (1.00h). In the following, whenever $ED_{50}$, $D_1$ or $D_2$ are mentioned in the text, these values are used, unless otherwise stated. This is in accordance with the FDA guideline (10), which allows for a choice of $D_1$ between 0.25-0.5 times $ED_{50}$ and of $D_2$ between 2-4 times $ED_{50}$.

To estimate the proportion of subjects expected to be detectors, values for $AUEC_{0-24h}$ at $D_1$ and $D_2$ were estimated by linear interpolation of the mean $AUEC_{0-24h}$ by duration curve (values in Table 20) and it was assessed how many of the subjects that would have been detectors if they had been included in the pivotal study. The result is shown in Table 22. Eight out of twelve subjects were found to be detectors, giving an estimate of 8/12 = 67% detectors.

Table 22: Mean chromameter $a^*$ $AUEC_{0-24h}$ by dose duration. Estimated detector status based on estimated $AUEC_{0-24h}$ at $D_1$ and $D_2$, pilot phase

<table>
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<th>$D_2$ (h)</th>
<th>$AUEC(D_2)$</th>
<th>$AUEC(D_2)$ / $AUEC(D_1)$</th>
<th>Detector (Y/N)</th>
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</tr>
</tbody>
</table>
**Pivotal Phase**

The primary criterion was the colorimetric parameter $a^*$. The mean of two successive measurements performed on each site was used. The variable subject to analysis was denoted $\Delta a^*$ and was computed by first subtracting the baseline values – i.e. the $a^*$ values immediately after removal of the application. Then, in this new data set, the mean values at the untreated control sites were subtracted separately for each arm. The area under the curve from 0 to 24 hours (AUEC$_{0\text{-}24h}$) for $\Delta a^*$ were calculated by the trapezoidal method for each individual test site. In Figure 6, $a^*$ values adjusted for baseline are plotted against time. The unadjusted values are tabulated in Table 23 using standard summary statistics. In the same way the adjusted values are tabulated in Table 24, while AUEC$_{0\text{-}24h}$ is tabulated in Table 25 using standard summary statistics. (The corresponding values for all randomised subjects are listed in Table 34, Table 35 and Table 36 in Section 18).

Figure 6: Mean chromometer $a^*$ adjusted for baseline per dose duration by measurement time: per protocol analysis set, pivotal phase
Table 23: Mean a* by treatment and assessment time: per protocol analysis set, pivotal phase

<table>
<thead>
<tr>
<th>Time after removal (h)</th>
<th>DAIVOBET/DOVOBET gel ED50</th>
<th>DIPROSONE ointment ED50</th>
<th>DIPROSONE ointment D1</th>
<th>DIPROSONE ointment D2</th>
<th>Untreated</th>
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Table 24: Mean Δa* (baseline adjusted and untreated control site corrected) by treatment and assessment time: per protocol analysis set, pivotal phase

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<th>DIPROSONE ointment D1</th>
<th>DIPROSONE ointment D2</th>
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<td>0.58</td>
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<td>-1.27</td>
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<td>1.65</td>
</tr>
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<td></td>
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<td>0.58</td>
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<tr>
<td><strong>T19H</strong></td>
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</tr>
<tr>
<td>Mean</td>
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<td>-0.68</td>
<td>-0.60</td>
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<td>-2.28</td>
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<tr>
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<td>0.93</td>
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<td>-1.07</td>
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<td>0.85</td>
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<tr>
<td>Min</td>
<td>-3.69</td>
<td>-4.66</td>
<td>-3.10</td>
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Table 25: Mean AUEC for Δa*(baseline adjusted and untreated control site corrected) by treatment: per protocol analysis set, pivotal phase

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<th>Min</th>
<th>Max</th>
<th>N</th>
</tr>
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<td>108</td>
</tr>
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</table>

Table 26 contains the results of a statistical analysis using Locke’s method (See Section 11.8.1.6.2) to estimate a confidence interval for the ratio of the expected AUEC0.24h for the treatment group and the expected AUEC0.24h for the untreated group.

Table 26: Results of the statistical analysis of bioequivalence based on chromameter a*: per protocol analysis set, pivotal phase

<table>
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<th>Ratio</th>
<th>90% confidence interval (Locke’s method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.78</td>
<td>(0.64, 0.95)</td>
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</tbody>
</table>

The estimate of the ratio was 0.78, with a 90% confidence interval of (0.64, 0.95), where the confidence level is 90%, as recommended in the FDA guidance (10). Since the interval is entirely below 1, this suggests that DAIVOBET/DOVOBET gel has less blanching effect than the reference ointment. A 95% confidence interval by Locke’s method is (0.61, 0.99). Testing whether the difference between DAIVOBET/DOVOBET and DIPROSONE is 0 with a t-test gave p=0.0450. Wilcoxon’s signed rank test gave p=0.0438. These results indicate a true difference in blanching effect so that DAIVOBET/DOVOBET gel causes less blanching than the reference ointment.
14.4.2 Secondary Response Criteria

Pilot Phase
For the visual blanching score, the analysed variable was the mean of the untreated control site corrected visual blanching scores (from 0 to 4) made by the two readers at each time point. In Figure 7 and Figure 8, mean visual scores and mean AUEC₀⁻²₄h are plotted. The uncorrected values are accounted for in Table 27 and the corrected values likewise in Table 28, while AUEC₀⁻²₄h of the visual blanching score is accounted for in Table 29.

Figure 7: Mean visual score per treatment by (untreated control site corrected) dose duration: per protocol analysis set, pilot phase
Figure 8: Mean AUEC$_{0-24h}$ for visual score (untreated control site corrected) by dose duration: per protocol analysis set, pilot phase
Table 27: Mean visual score by treatment and assessment time: per protocol analysis set, pilot phase

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Table 28: Mean visual score (untreated control site corrected) by treatment and assessment time: per protocol analysis set, pilot phase

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Table 29: Mean AUEC₀-2₄₉ for visual score (untreated control site corrected) by treatment: per protocol analysis set, pilot phase

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</table>

A dose duration-response curve was fitted. As a sensitivity analysis, ED₅₀, D₁ and D₂ were estimated. The result is shown in Table 30. Even though ED₅₀, D₁ and D₂ were estimated separately for the secondary response criterion, for practical reasons, the same application times as for the primary criterion were used when the visual score was assessed, i.e. ED₅₀=20 min (0.33h), D₁=5 min (0.08h), D₂=60 min (1.00h).

Table 30: Parameter estimates from Emax model fitted by nonlinear least squares regression with AUEC₀-2₄₉ of the visual score as dependent variable, pilot phase

<table>
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<tr>
<th>Emax</th>
<th>ED₅₀ (h)</th>
<th>D₁ (h)</th>
<th>D₂ (h)</th>
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<tr>
<td>36.42</td>
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</table>

Pivotal Phase

For the visual blanching score, the analysed variable was the mean of the visual blanching scores (from 0 to 4) between the two readers for each time point. In Figure 9, mean visual scores are plotted. The uncorrected values appear in Table 31, using standard summary statistics and the corrected values likewise in Table 32, while AUEC₀-2₄₉ of the visual
blanching score appear in Table 33. (The corresponding values for all randomised subjects are listed in Table 37, Table 38 and Table 39 in Section 18).

The visual score shows the same tendency as a* as is seen in Figure 9.

Figure 9: Mean visual score per treatment by measurement time: per protocol analysis set, pivotal phase
Table 31: Mean visual score by treatment and assessment time: per protocol analysis set, pivotal phase

<table>
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<th>Time after removal (h)</th>
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Table 32: Mean visual score (untreated control site corrected) by treatment and assessment time: per protocol analysis set, pivotal phase

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<th>Time after removal (h)</th>
<th>DAIVOBET/DOVOBET ointment</th>
<th>DIPROSONE ointment ED50</th>
<th>DIPROSONE ointment D1</th>
<th>DIPROSONE ointment D2</th>
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<td>Mean (DIPROSONE ointment ED50)</td>
<td>Mean (DIPROSONE ointment D1)</td>
<td>Mean (DIPROSONE ointment D2)</td>
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<td>Min</td>
<td>Max</td>
<td>N</td>
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<td>108</td>
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<td>1.0</td>
<td>108</td>
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<td>T4H</td>
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Table 33: Mean AUEC\textsubscript{0-24h} for visual score (untreated control site corrected) by treatment: per protocol analysis set, pivotal phase

<table>
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<tr>
<th>Treatment</th>
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<th>ED50</th>
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<th>D2</th>
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<td>DIPROSONE ointment D2</td>
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<tr>
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<td>39.8</td>
<td>45.0</td>
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</table>

As shown in Table 33, the results of the visual score also indicate that the skin blanching after DAIVOBET/DOVOBET gel is less than after DIPROSONE ointment.

14.4.3 Statistical/Analytical Issues
See Statistical Appendix, Appendix IV.

14.4.4 Concomitant Treatment
At all visits, the use of concomitant medications was recorded. These medications were coded according to the WHO ATC Classification System. Concomitant medication at baseline is tabulated in Table 9 (pilot phase) and Table 17 (pivotal phase). For more details, see Appendix XI listing 17, pilot phase, and listing 17, pivotal phase.

14.5 PHARMACODYNAMIC CONCLUSIONS
Bioequivalence cannot be claimed from the results of this study. The 90% confidence interval for the ratio is entirely below 1, which indicates that DAIVOBET/DOVOBET gel gives less blanching than the reference ointment. This conclusion is also supported by a 95% confidence interval for the ratio and from standard parametric and non-parametric tests of equality of the means (t-test and Wilcoxon’s signed rank test).
15 SAFETY EVALUATION

15.1 DURATION AND EXTENT OF EXPOSURE TO TREATMENT WITH TRIAL MEDICATION

Pilot Phase
The reference ointment was applied at sites determined by the randomisation scheme in staggered applications at durations from 0.25 hours to 6 hours. Each subject was exposed to 8 x 10 mcl single applications of DIPROSONE ointment.

Pivotal Phase
DAIVO BET/DOVO BET gel and the reference ointment were applied at sites determined by the randomisation scheme, the DAIVO BET/DOVO BET gel with duration ED₅₀ as determined in the pilot phase and the DIPROSONE ointment with durations D₁, D₂ and ED₅₀ as determined in the pilot phase. Each subject was exposed to 4 x 10 mcl single applications of DAIVO BET/DOVO BET gel and 8 x 10 mcl single applications of DIPROSONE ointment.

15.2 ADVERSE EVENTS REPORTED
Adverse events, as described by investigators, were categorised according to MedDRA version 6.1. All categorisation was done prior to unblinding the study.

Pilot Phase
There were no adverse events reported.

Pivotal Phase
One subject had two adverse events reported: one nasopharyngitis (common cold), which was deemed to be unrelated and one urticaria (urticaria flare), which was considered as possibly related. Both adverse events were mild.

For more details, see Appendix XI listing 18, pivotal phase.

15.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS
No death, no other serious adverse event and no other significant adverse event were reported in the study.
15.4 LABORATORY DATA
Not applicable.

15.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY
No signs of local irritation were reported.

15.6 SAFETY CONCLUSIONS
Under the conditions of the study, DAIVOBET/DOVOBET gel and DIPROSONE ointment were found to be safe and well tolerated.
16 DISCUSSION

16.1 SUMMARY OF RESULTS
For the primary response criterion, the colorimetric parameter a*, DAIVOBET/DOVOBET gel was found not to be bioequivalent to the reference product DIPROSONE ointment. The results of the visual scoring supported this conclusion. Both products were safe and well tolerated.

16.2 DESIGN AND CONDUCT OF THE STUDY
The vasoconstrictor bioassay has been adopted by the FDA as a mean for assessing bioequivalence of topical corticosteroids. The FDA Guidance recommends that a pilot dose duration–response study has to be performed with the reference product to determine the optimal dose duration of the pivotal bioequivalence study.

A pilot study for the determination of the dose duration-response curve with the commercially available product DIPROSONE ointment was performed in 12 healthy volunteers according to the FDA guidance. The pilot study served to estimate the dose duration ED₅₀ for the following in vivo bioequivalence study comparing the betamethasone dipropionate in DAIVOBET/DOVOBET gel with the betamethasone dipropionate in DIPROSONE ointment (10). Twelve responder subjects (8 females and 4 males, aged 23 to 40 years) were randomised and completed the pilot phase.

The primary variable was the colorimetric parameter a* adjusted to baseline and to the untreated controls (Δa*). The area under the curve (AUEC₀-2₄h) was calculated for each dose duration. The estimated dose duration ED₅₀ was short: 0.24 hour.

This short ED₅₀ was in accordance with data from the literature. The more potent the corticosteroid, the shorter the ED₅₀ (13).

According to the guidelines, ED₅₀, D₁ and D₂ were estimated and the pivotal phase was performed with ED₅₀ rounded up to 20 minutes, D₁ equal to 5 minutes and D₂ equal to 1 hour.

The sample size calculation for the pivotal phase was based on the detector rate estimated in the pilot part of the present study (8/12 = 67%) to expect 40-60 evaluable subjects as recommended in the FDA guideline.
The same rate of detectors as in the pilot part of the present study was found in the MCB 9902 FR study (8/12 = 67%) (12) which is also comparable to the sample size assumption made based on the detector rate in the FDA guideline example (7/12 = 58% detectors).

In the pivotal part of the study, seventy (70) responders were randomised in the study and only 27 were found to fulfil the criterion for detectors – a rate of detectors of 39%. This rate of detectors was similar to what was found in the pivotal part of a similar study with DAIVOBET/DOVOBET ointment (the MCB 9902 FR study) (12) (36%).

16.3 INTERPRETATION OF STUDY RESULTS

Up to now, there are very few reports in the literature on the bioequivalence of topical corticosteroid formulations based on the proposed methodology recommended in the FDA Guidance. In a previous published study designed to determine if an ointment containing calcipotriol with betamethasone dipropionate (DAIVOBET/DOVOBET® ointment) was bioequivalent to a reference formulation containing betamethasone dipropionate alone (12), the ED_{50} was estimated to about one hour, which was three times longer than the estimated ED_{50} in the current study.

It should be mentioned that in the few published studies the number of detectors was smaller than required in the FDA guidance (40-60 detectors).

In the present study, 70 responders were randomised and only 27 (39%) subjects fulfilled the criterion for detectors. On the basis of the detector population, DIPROSONE ointment and DAIVOBET/DOVOBET gel were found not to be bioequivalent, as the 90% confidence interval for blanching effect was below 1 (0.64 to 0.95).

Values for population ED_{50} decreases with increase in corticosteroid product potency (13). For potent corticosteroid formulations, the ED_{50} values are very short so that D_{1} and D_{2} are very close to each other and only a small number of responder subjects have a D_{2}/D_{1} AUECs ratio ≥ 1.25.

The responder status is determined by the ability of a subject to express a clear-cut visually assessed blanching effect. Highly reactive subjects may thus be selected by the investigator but such subjects can be a posteriori poor detectors.
The screening procedure discards subjects who are poor responders as supposed to be non detectors.

Moreover, for potent corticosteroids the screening procedure with dose duration equal to 4-6 hours seems not really appropriate when compared to the bioequivalence study in which dose durations are very short (less than one hour).

However on the basis of the study data, it can be concluded that the betamethasone dipropionate in DAIJOBET/DOVOBET gel did not prove to be bioequivalent with the reference product DIPROSONE ointment.

This result was expected as DAIJOBET/DOVOBET gel showed a significantly lower antipsoriatic effect than DAIJOBET/DOVOBET ointment (for which bioequivalence to DIPROSONE ointment has been demonstrated (12)) in a psoriasis plaque test study (14).

17 CONCLUSIONS

The study was conclusive and demonstrated that DAIJOBET/DOVOBET gel was not bioequivalent to DIPROSONE ointment regarding AUEC0-24h for the colorimetric parameter Δa* (baseline adjusted and untreated control site corrected).

DAIJOBET/DOVOBET gel induced less skin blanching than DIPROSONE ointment, suggesting that DAIJOBET/DOVOBET gel can be considered a weaker (less clinically potent) topical corticosteroid than DIPROSONE ointment.
18 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

All tabulations in this section concern the pivotal phase of the study.

Table 34: Mean $a^*$ by treatment and assessment time: randomised subjects, pivotal phase

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<th>Time after removal (h)</th>
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Table 35: Mean Δa* (baseline adjusted and untreated control site corrected) by treatment and assessment time: randomised subjects, pivotal phase

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Table 36: Mean AUEC\textsubscript{0-24h} for Δa* (baseline adjusted and untreated control site corrected) by treatment: randomised subjects, pivotal phase

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Table 37: Mean visual score by treatment and assessment time: randomised subjects, pivotal phase

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Table 38: Mean visual score (untreated control site corrected) by treatment and assessment time: randomised subjects, pivotal phase

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Table 39: Mean AUEC_{0-24h} for visual score (untreated control site corrected) by treatment: randomised subjects, pivotal phase

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Table 40: Mean L* by treatment and assessment time: randomised subjects, pivotal phase

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19 REFERENCES


2. Declaration of Helsinki, 18th World Medical Assembly, Helsinki, Finland 1964, amended by the 29th WMA Tokyo 1975, the 35th WMA Venice 1983, the 41st WMA Hong Kong 1989, the 48th WMA Somerset West 1996 and the 52nd WMA Edinburgh 2000.


20 LIST OF APPENDICES

Appendix I: Study Protocol, appendix version 2.0
Appendix II: Case Report Form, appendix version 2.0
Appendix III: Statistical Analysis Plan, appendix version 2.0
Appendix IV: Statistical Appendix, version 1.0
Appendix V: Representative Patient Information and Informed Consent (ICTM master version), appendix version 2.0
Appendix VI: List of IECs/IRBs consulted and copy of all approvals/favourable opinions, appendix version 2.0
Appendix VII: List of Investigators and Summary CVs, appendix version 2.0
Appendix VIII: List of Subinvestigators, appendix version 2.0
Appendix IX: List of LEO staff members contributing to the trial, appendix version 2.0
Appendix X: Audit Certificate(s) (not applicable)
Appendix XI: Individual Patient Data, appendix version 2.0
Appendix XII: Confirmation of Statistical Information Form, appendix version 2.0
Clinical Study Report MBL 0403 FR In vivo bioequivalence study of betamethasone dipropionate in DAIVOBET/DOVOBET gel and DIPROSONE ointment according to FDA guideline for vasoconstrictor bioassay 20-Mar-2007

eDoc LEO RD 00065295
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## Approvals

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