### 3 SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Manufacturer:</th>
<th>Location of study report in Regulatory Dossier (For National Authority Use only)</th>
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<tbody>
<tr>
<td>LEO Pharma A/S</td>
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<table>
<thead>
<tr>
<th>Name of Investigational Product/Finished Product, if available:</th>
<th>Volume:</th>
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<tbody>
<tr>
<td>DAVIOBET/DOVOBET gel</td>
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<table>
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<tr>
<th>Name of Active Substance:</th>
<th>Page:</th>
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<tbody>
<tr>
<td>Calcipotriol plus betamethasone dipropionate</td>
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<tr>
<th>Title of study/Protocol Code Number:</th>
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<tbody>
<tr>
<td>Repeat insult patch test with DAVIOBET/DOVOBET gel including 21-days cumulative irritation study and sensitisation potential in 200 healthy subjects.</td>
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**SPONSOR ref.:** MBL 0302 FR

**International Co-ordinating Investigator:**

Didier Chassard, MD.

**Centre details:**

Single centre study conducted by [Redacted], France and [Redacted], France.

**Publication references:**

Not applicable.

**Study period details:**

Date of first subject enrolment 18-Apr-2005, and date of last subject completed 03-Aug-2005.

**Phase of development:**

**Objectives/hypothesis:**

The objective of this study was to determine the skin irritation potential and sensitisation potential of DAVIOBET/DOVOBET gel and the gel vehicle after repeated application on the skin of healthy subjects.

**Study methodology:**

This was a phase I, single-centre, randomised, double-blinded, vehicle-controlled study with intra-individual comparison of DAVIOBET/DOVOBET gel versus the gel vehicle. 220 subjects were enrolled by the investigator in order to reach 200 evaluable subjects who completed the challenge phase according to per protocol requirements.

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The duration of the study for each subject was 6 to 8½ weeks, consisting of a 2-week run-in period if required, followed by a 3-week induction phase and a one week challenge phase, separated by a 2-week rest phase. A follow-up visit was performed 2 weeks after the subject's last on-treatment visit in the event of an ongoing adverse event. Six subjects had a follow-up visit.

All topical applications were performed on the skin of the back using occlusive dressings (Large Finn Chambers®).

For each application fifty (50) ml of the investigational products were delivered directly into a Finn Chamber® patch-test using a micropipette (Eppendorf®).

**The Induction phase (Days 1-21):** A total of 15 applications were performed over a 21-day period distributed as five applications per week (every day except weekends) to two selected test sites on the left side of the back. All subjects received both investigational products according to randomisation (site 1/site 2). Clinical assessments of reactions were performed for each site on the day after each application, approximately 30 minutes after removal of the occlusion, before the following application.

**The Rest phase (Days 22-35):** 2 weeks without any application.

**The Challenge phase (Days 36-40):** The products were applied to two new test sites on the right of the back on Day 36 and remained on the skin for 48 hours. The test sites were scored (after removal of the patches) on Day 38 and again on Days 39 and 40 (corresponding to further 24- and 48-hour periods, respectively).

**A follow-up visit** took place 2 weeks after the subject’s last on-treatment visit if any adverse event (serious or non-serious) classified as possible or probably related to the study medication or not assessable in relation to the study medication was ongoing at the subject’s last on-treatment visit.

Skin irritation potential and sensitisation potential were based on an assessment using a visual scoring of the skin reaction. The evaluations were done approximately 30 minutes after removal of the patches. In addition, in the challenge phase, clinical scoring was repeated approximately 24 and 48 hours after removal of the patches.

**The Rechallenge phase (Day 47):** Any subject whose sensitisation reaction was judged as equivocal after challenge on Day 40 was re-challenged after approximately one-week rest period under the same conditions as for the challenge, using a new naive patch site, under the same condition as for Day 36.
Name of Sponsor/Manufacturer: LEO Pharma A/S

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

Name of Active Substance: Calcipotriol plus betamethasone dipropionate

Number of patients enrolled: 220.

Diagnosis and main criteria for patient selection:
The subjects to be included in this study should be healthy as defined by medical history and a physical examination (including blood pressure and urine pregnancy test for the females) made prior to inclusion.

Subjects should be 18 to 65 years old and willing to give written informed consent.

Investigational product, dose, method of administration, lot numbers:
Product name: DAIVOBET/DOVOBET gel (calcipotriol 50 mcg/g and betamethasone 0.5 mg/g as dipropionate)
Unit dose: 50 ml
Regimen: Sixteen applications in total.
  During the induction phase: Five applications per week, for 3 weeks (twelve repeated 24-hour topical applications and three 72-hour applications were performed on the same sites).
  During the challenge phase: One 48-hour topical application.
Mode/Route: Topical, occlusive
Batch number: [redacted]/08 2006

Reference product, dose, method of administration, lot numbers:
Product name: Gel vehicle
Unit dose: 50 ml
Regimen: Sixteen applications in total.
  During the induction phase: Five applications per week, for 3 weeks (twelve repeated 24-hour topical applications and three 72-hour applications were performed on the same sites).
  During the challenge phase: One 48-hour topical application.
Mode/Route: Topical, occlusive
Batch number: [redacted]/08 2006
**Name of Sponsor/Manufacturer:** LEO Pharma A/S  
**Location of study report in Regulatory Dossier for authorities:**  
**Name of Investigational Product/Finished Product, if available:** DAIVO BET/DOVOBET gel  
**Name of Active Substance:** Calcipotriol plus betamethasone dipropionate  
**Volume:**  
**Page:**

**Duration of treatment:**
Twenty-one (21) days plus a final 48-hour application after a rest period of 2 weeks. If equivocal, a re-challenge of new naive sites after an additional 1-week rest.

**Criteria for evaluation:**
- **Skin irritation and sensitisation:** Skin irritation was assessed by visual scoring on a 5-point scale from 0 (no erythema) to 4 (severe erythema, oedema, vesicles or blisters).
- Skin irritation potential was determined using the Cumulative Irritancy Index (CII) calculated for each of the two products on the basis of the visual scorings performed during the induction phase.
- Sensitisation potential was evaluated by the investigator’s assessment concerning a possible sensitisation reaction as negative (0), equivocal (1) or positive (2) of each site at the end of the challenge phase (Day 40).

**Safety:**
Monitoring for the occurrence of adverse events (AEs), changes in physical examination and vital signs (blood pressure and pulse rate).

**Statistical methodology**
Descriptive statistics accompanied all analyses if not otherwise indicated. These statistics include n, mean, standard deviation, minimum, median, and maximum for continuous parameters. Categorical and ordinal scale parameters were summarised with frequencies and treatment percentages.

Skin irritation potential and sensitisation potential analysis were performed on the Per Protocol population. Results for visual scoring of skin irritation and for investigator’s assessment of sensitisation are listed by subject and treatment.

Visual scorings are presented per treatment and time-point using descriptive statistics on raw data and changes from baseline.

For each subject, the maximum visual scoring during the induction phase and during the challenge phase is listed.

For each subject a Cumulative Irritancy Index (CII) was calculated for each of the two products: CII = Sum of scores across readings (Day 2-22)/number of readings.

A Mean Cumulative Irritancy Index (MCII) was calculated for each product by averaging individual CIIs across subjects.
The MCII was used to evaluate the skin irritation potential of the product. MCII is presented using descriptive statistics and bar charts.

A frequency table presenting the count and frequency of subjects by category of sensitisation (negative/positive) and treatment is provided. Proportion of each sensitisation category is presented graphically per treatment using bar charts.

**Summary – Conclusions:**

**Skin irritation and sensitisation results:**

Under the conditions of this study, DAIVOBET/DOVOBET gel and gel vehicle were demonstrated to have no irritation potential. All subjects but one were scored 0 (no erythema) or 1 (slight erythema with or without oedema). Only one subject was scored 4 (severe erythema, oedema, vesicles or blisters) after DAIVOBET/DOVOBET gel application on day 15.

Moreover, no sensitisation potential was shown for any of the study products as for all subjects in both groups the sensitisation reaction scores were negative.

**Safety results:**

No serious adverse events were reported and no subjects were discontinued from the study for reasons related to the study treatment.

One subject was withdrawn from the study because of a gastroenteritis which was not related to the study treatment.

Six non treatment-emergent adverse events, all of mild intensity, and 38 treatment emergent adverse events (32 of mild intensity and 6 of moderate intensity) were reported.

During the study, 8 subjects reported 9 adverse events on the application site, of which 8 were reported on the DAIVOBET/DOVOBET gel application site and one on the gel vehicle application site. Eight of these adverse events were considered as related to the study treatment and one as not related to the study treatment.

Moreover, 23 subjects reported 29 systemic adverse events, all of which were considered as not related to the study treatment.

Neither trends nor relevant changes from baseline were observed in vital signs and physical examination.
In summary, repeated application of 50 mcl DAIVOBET/DOVOBET gel or gel vehicle using Finn Chambers® was safe and well tolerated.

Conclusion:
This study has shown that:
- DAIVOBET/DOVOBET gel and gel vehicle are not irritating,
- DAIVOBET/DOVOBET gel and gel vehicle have no sensitisation potential,
- Repeated application of 50 mcl DAIVOBET/DOVOBET gel or gel vehicle using Finn Chambers® is safe and well tolerated.
### 3.1 SCHEDULE/CHART OF STUDY PROCEDURES

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening period</th>
<th>Induction phase (Week 1-3)</th>
<th>Rest period (Week 4-5)</th>
<th>Challenge phase (Week 6)</th>
<th>Follow up visit</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
<td>Day 4</td>
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<td>Urine pregnancy test (only for females)</td>
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</table>

1. Screening period was performed within 2 weeks or on Day 1 before the first application.
2. First application of induction phase and application of challenge phase were made on healthy skin (score 0).
3. Scorings were performed approximately 30 minutes after each removal. During the induction phase, if an unacceptable reaction was observed (score 4), no further testing took place and the test site was scored 4 for each remaining day of the 21-day test period.
4. If a subject missed a visit, a replacement application was performed during the rest phase.
5. Follow-up visit was performed 2 weeks after the subject’s last on-treatment visit only if a serious adverse event or a non-serious adverse event classified as possibly/probably related to the study medication or not assessable was ongoing at the last visit.