### 3 SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Manufacturer:</th>
<th>Location of study report in Regulatory Dossier for authorities</th>
<th>(For National Authority Use only)</th>
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<tbody>
<tr>
<td>LEO Pharma A/S</td>
<td>Volume:</td>
<td></td>
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<tr>
<td>Name of Investigational Product/Finished Product, if available:</td>
<td>Name of Active Substance:</td>
<td>Page:</td>
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<tr>
<td>DAIVOBET/DOVOBET gel</td>
<td>Calcipotriol plus betamethasone dipropionate</td>
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<tr>
<td>Title of study/Protocol Code Number:</td>
<td>In vivo bioequivalence study of betamethasone dipropionate in DAIVOBET/DOVOBET gel and DIPROSONE ointment according to FDA Guideline for vasoconstrictor bioassay.</td>
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**Centre details:**

The trial was conducted in France

**Publication references:**

No publication planned

**Study period details:**

<table>
<thead>
<tr>
<th>Phase of development:</th>
<th>Phase I/IIa (pharmacodynamic study)</th>
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<tr>
<td>Pilot Phase:</td>
<td></td>
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<tr>
<td>First subject enrolled on 07 March 2005</td>
<td>Last subject completed on 18 March 2005</td>
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<tr>
<td>Pivotal Phase:</td>
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<tr>
<td>First subject enrolled on 02 May 2005</td>
<td>Last subject completed on 17 June 2005</td>
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**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\textsubscript{50} 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\textsubscript{2}/D\textsubscript{1} 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
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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.
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.
**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

**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:** DAIVOBET/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 mcl 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 mcl 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 mcl 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).
Duration of treatment:

**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 (DAIVOBET/DOVOBET gel) was applied on four sites for duration equal to ED$_{50}$. DIPROSONE ointment was applied on eight sites for durations equal to D$_{1}$ (two sites), to ED$_{50}$ (four sites) and to D$_{2}$ (two sites). According to the FDA guidance, the pivotal study was performed with the ED$_{50}$ value determined in the pilot study. The determination of D$_{1}$ and D$_{2}$ was based on the ED$_{50}$ 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 (AUEC$_{0-24h}$) 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 AUEC$_{0-24h}$ (model of FDA guideline).
**Summary - Conclusions**

**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 (7 females, 5 males) aged 23-40 years (mean: 30.9 ± 5.9) were randomised and completed the study.

The ED$_{50}$ estimated from $E_{\text{max}}$ model fitted by nonlinear least squares regression was equal to $0.24$ h (14 min), $D_1$ to $0.12$ h (7 min) and $D_2$ to $0.48$ h (29 min).

For practical reasons, the values used in the pivotal phase were: ED$_{50} = 20$ min., $D_1 = 5$ min. and $D_2 = 60$ 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 AUEC$_{0-24h}$ for $\Delta a^*$ (baseline adjusted and untreated control site corrected) by treatment are reported in the table below for the per protocol analysis set:

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<thead>
<tr>
<th></th>
<th>DAIVOBET/DOVOBET gel</th>
<th>DIPROSONE ointment</th>
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<tbody>
<tr>
<td></td>
<td>ED$_{50}$</td>
<td>ED$_{50}$</td>
</tr>
<tr>
<td>N (1)</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>Mean</td>
<td>-10.03</td>
<td>-12.89</td>
</tr>
<tr>
<td>Std</td>
<td>10.87</td>
<td>12.87</td>
</tr>
<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>
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(1) Number of sites

At a dose duration of 20 minutes (ED$_{50}$) determined from the pilot study
Name of Sponsor/Manufacturer: LEO Pharma A/S

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Name of Active Substance: Calcipotriol plus betamethasone dipropionate

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.

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<tr>
<td></td>
<td>ED50</td>
<td>ED50</td>
</tr>
<tr>
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<td>Min</td>
<td>-6.1</td>
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<tr>
<td>Max</td>
<td>39.8</td>
<td>45.0</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 ∆a* (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