## 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>
</tr>
</thead>
<tbody>
<tr>
<td>LEO Pharma A/S</td>
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<tr>
<td>Name of Investigational Product/Finished Product, if available:</td>
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<tr>
<td>Dovobet®, Daivobet®</td>
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<td>Name of Active Substance:</td>
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<tr>
<td>Calcipotriol + betamethasone dipropionate</td>
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<tr>
<td>Title or study/Protocol Code Number:</td>
<td>Repeated courses of calcipotriol/betamethasone dipropionate in psoriasis vulgaris /MCB 0102 INT</td>
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<tr>
<td>International Co-ordinating Investigator:</td>
<td>Professor</td>
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<td>Centre details:</td>
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<td>There were a total of 67 centres, 5 in Belgium, 7 in Canada, 2 in Denmark, 4 in Finland, 13 in France, 3 in Germany, 3 in Ireland, 4 in Norway, 3 in Spain, 4 in Sweden and 19 in the United Kingdom</td>
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<td>Publication references:</td>
<td>Not applicable</td>
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<td>Study period details:</td>
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<tr>
<td>23-Aug-2002 to 20-Apr-2004; total duration of 20 months</td>
<td>Phase of development: Phase III</td>
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<td>Objectives:</td>
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<td>To determine the safety and efficacy of the following in the treatment of patients with psoriasis vulgaris: 52 weeks of combination (calcipotriol + betamethasone dipropionate) treatment; 52 weeks of alternating 4 week periods of combination/calcipotriol treatment; 4 weeks of combination treatment followed by 48 weeks of calcipotriol treatment.</td>
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<td>Study methodology:</td>
<td>An international, multicentre, prospective, randomised, double-blind, 3 arm, parallel group, 52 week safety study. Patient with psoriasis vulgaris were randomised in a 1:1:1 ratio to one of the three treatment groups described above. Every 4 weeks investigators assessed adverse events and the global disease severity on a 6 category scale (disease absent to very severe), and patients assessed study treatment as either satisfactory or not satisfactory. Adrenal function testing was performed at week 0, 4, 12, and end of study in patients at UK centres.</td>
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<tr>
<td>Number of patients enrolled:</td>
<td>636 enrolled, 634 randomised: 212 to the combination group, 213 to the combina-</td>
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</table>
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Name of Investigational Product/Finished Product, if available: Dovobet®, Daivobet®

Name of Active Substance: Calcipotriol + betamethasone dipropionate

All randomised patients were included in the ITT analysis set; 626 patients were included in the safety analysis set: 207 in the combination group, 213 in the combination/calcipotriol (4/4 alt.) group and 206 in the combination/calcipotriol (4/48) group.

Diagnosis and main criteria for patient selection:
Patients ≥ 18 years of age with a diagnosis of psoriasis vulgaris of the body of at least moderate severity and amenable to topical treatment were selected. Patients with any of the following were excluded: more than 30% of body surface area affected; erythrodermic, exfoliative or pustular psoriasis; concurrent use of anti-psoriatic treatments (systemic, topical or UV); disorders of calcium metabolism; other skin conditions present on psoriatic areas of the body.

Investigational product, dose, method of administration, lot numbers:
Combination (calcipotriol 50μg/g + betamethasone dipropionate 0.5mg/g) ointment applied once daily as required. See 'Objectives' section for the treatment group regimens. Lot numbers: 

Reference product, dose, method of administration, lot numbers:
Calcipotriol 50μg/g ointment applied once daily as required. See 'Objectives' section for the treatment group regimens. Lot numbers:

Duration of treatment:
52 weeks

Criteria for evaluation
Efficacy: The investigators' global assessment of disease severity (with disease absent, very mild or mild being considered as 'satisfactory') and the patients' global assessment of study treatment (secondary response criteria).
Safety: Adverse drug reactions of any type and adverse events of concern associated with long term topical corticosteroid use where relationship to study medication was at least a reasonable possibility as identified by an independent Adjudication Panel (primary response criteria) and adverse events of any type, weight of study medication used, reasons for withdrawal and results of adrenal function tests (secondary response criteria).

Statistical methodology:
Safety data were presented for the safety analysis set, efficacy data were presented for the intention-to-treat analysis set.
The proportion of patients who experienced adverse drug reactions of any type during the study was compared for all three pairwise treatment group comparisons using the chi-square test.

The proportion of patients with adverse events of concern associated with long term topical corticosteroid use where relationship to study medication was at least a reasonable possibility was compared for all three pairwise treatment group comparisons using Fisher's exact test.

The percentage of assessments across visits defined as 'satisfactory' by the investigators' global assessment of disease severity and by the patients' global assessment of study treatment were compared across treatment groups using the Kruskall-Wallis test for the overall treatment effect and the Wilcoxon rank-sum test for each pairwise treatment group comparison. This was a change from the protocol-specified analysis (analysis of variance) because the data were skewed and was addressed in the statistical analysis plan prior to unblinding.

Summary - Conclusions:

The mean age of randomised patients was 48.8 years, 61.0% were male, 97.3% were caucasian and 69.1% had psoriasis of a moderate severity at visit 1.

Efficacy results:

The overall test of treatment effect for the percentage of satisfactory assessments across visits for the investigators' global assessment of disease severity showed a trend towards a difference between treatments (P = 0.071), which appeared to be due to the comparison of the combination and combination/calcipotriol (4/48) groups (P = 0.025).

The median percentage was 84.0 in the combination group, 75.0 in the combination/calcipotriol (4/4 alt.) group, and 70.0 in the combination/calcipotriol (4/48) group.

The number of patients with 100% satisfactory assessments during the study were 76 (35.8%) in the combination group, 59 (27.7%) in the combination/calcipotriol (4/4 alt.) group, and 51 (24.4%) in the combination/calcipotriol (4/48) group. It is concluded that there is a trend in favour of the combination group compared to the combination/calcipotriol group.

The overall test of treatment effect for the percentage of satisfactory assessments across visits for the patients' global assessment of study treatment showed a trend towards a difference between treatments (P = 0.071), which appeared to be due to the comparison of the combination and combination/calcipotriol (4/48) groups (P = 0.036) and the combination and combination/calcipotriol (4/4 alt.) groups (P = 0.061). The
median percentage was 87.3 in the combination group, 76.9 in the combination/calcipotriol (4/4 alt.) group, and 83.3 in the combination/calcipotriol (4/48) group. The number of patients with 100% satisfactory assessments during the study were 80 (37.7%) in the combination group, 61 (28.6%) in the combination/calcipotriol (4/4 alt.) group, and 60 (28.7%) in the combination/calcipotriol (4/48) group. It is concluded that there is a trend in favour of the combination group compared to the combination/calcipotriol (4/48) group.

Safety results:
There were 58 ADRs in 45 (21.7%) patients in the combination group, 89 in 63 (29.6%) patients in the combination/calcipotriol (4/4 alt.) group, and 111 in 78 (37.9%) patients in the combination/calcipotriol (4/48) group. The odds ratio for an ADR in the combination group relative to the combination/calcipotriol (4/48) group was 0.46 (95% CI 0.30 to 0.70; P<0.001). In addition to psoriasis, the most common ADRs were those related to irritation of the skin (burning, pruritus, erythema). The Adjudication Panel identified ADRs of concern associated with long term topical corticosteroid use. There were 11 such ADRs in 10 (4.8%) patients in the combination group, 7 in 6 (2.8%) patients in the combination/calcipotriol (4/4 alt.) group, and 6 in 6 (2.9%) patients in the combination/calcipotriol (4/48) group. No statistically significant differences were found between the treatment groups. Skin atrophy was identified in 4 (1.9%) patients in the combination group, 1 (0.5%) in the combination/calcipotriol (4/4 alt.) group and 2 (1.0%) in the combination/calcipotriol (4/48) group. There were 379 adverse events in 137 (66.2%) patients in the combination group, 439 in 146 (68.5%) patients in the combination/calcipotriol (4/4 alt.) group, and 444 in 151 (73.3%) patients in the combination/calcipotriol (4/48) group. The most common events were nasopharyngitis, pruritus and psoriasis.

There were no patient deaths during the study. Thirty-nine serious adverse events were reported for 29 patients in the study. All the events were considered unrelated to study treatment, apart from three events of psoriasis: one in a patient in the combination group, and one in each of two patients in the combination/calcipotriol (4/48) group. All these three events resolved.

In the combination group, 64 (30.2%) randomised patients withdrew from the study, compared to 56 (26.3%) in the combination/calcipotriol (4/4 alt.) group and 70 (33.5%) in the combination/calcipotriol (4/48) group. In terms of patients withdrawing
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Due to adverse events, the figures were 14 (6.6%) patients in the combination group, 11 (5.2%) in the combination/calcipotriol (4/4 alt.) group and 16 (7.7%) in the combination/calcipotriol (4/48) group.

During the whole study, the mean weight of study medication used per patient was 898.8g in the combination group, 892.5g in the combination/calcipotriol (4/4 alt.) group, and 1044.0g in the combination/calcipotriol (4/48) group.

Nineteen patients underwent laboratory testing of adrenal function, 7 in the combination group, 6 in the combination/calcipotriol (4/4 alt.) group and 6 in the combination/calcipotriol (4/48) group. Only one patient had evidence of adrenal suppression of possible clinical significance post visit 1, and this patient was in the combination/calcipotriol (4/48) group; this event appeared after 11 months of calcipotriol treatment.

**Conclusion:**
Combination treatment for up to 52 weeks would appear to be safe and well tolerated whether used on its own or alternating every 4 weeks with calcipotriol treatment. There is a trend towards the efficacy of combination treatment used on its own for up to 52 weeks being better than that of 4 weeks combination treatment followed by 48 weeks of calcipotriol treatment.

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**Report date:**
24-Aug-2004