### Synopsis

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<th>Name of Sponsor/Company:</th>
<th>Individual Trial Table Referring to Part of the Dossier (For National Authority Use only)</th>
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<td>LEO Pharma A/S</td>
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<tr>
<th>Name of Finished Product:</th>
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<td>LEO 90105 ointment</td>
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<td>Calcipotriol hydrate plus betamethasone dipropionate</td>
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#### Title of trial:
Efficacy and safety of LEO 90105 ointment (calcipotriol hydrate plus betamethasone dipropionate) in Japanese subjects with psoriasis vulgaris

#### Trial centres:
The study was conducted at 69 sites in Japan.

#### Publication (reference):
Not applicable.

#### Trial period (years):
First subject enrolled on 06-Aug-2011
Last subject completed on 28-May-2012

Phase of development: 3

#### Objectives:
**Primary:** To compare the clinical efficacy of LEO 90105 ointment applied once daily with Dovonex® ointment applied twice daily and with Rinderon®-DP ointment applied once daily in Japanese subjects with psoriasis vulgaris.

**Secondary:** To compare the safety of LEO 90105 ointment applied once daily with Dovonex® ointment applied twice daily and with Rinderon®-DP ointment applied once daily in Japanese subjects with psoriasis vulgaris.

#### Methodology:
This was a national, multi-centre, prospective, randomised, double-blind, active-controlled, 3-arm, parallel group, 4 week study. Eligible subjects were randomised to receive one of the following three treatments for up to 4 weeks (in a 1:1:1 ratio): (1) LEO 90105 ointment and vehicle of LEO 90105 ointment once daily, (2) Dovonex® ointment twice daily, or (3) Rinderon®-DP ointment and vehicle of Rinderon®-DP ointment once daily. The medications were applied to psoriasis of the trunk/limbs. The study comprised four visits: Days 0, 7 (±1 day), 14 (±2 days), and 28 (±2 days) (Visits 1-4). Subjects who were considered by the (sub)investigator to require no further treatment before the end of 4 weeks’ treatment were to complete the study at this time.

#### Number of subjects (planned and analysed):
A total of 660 subjects were planned to be randomised in this study, and 676 were actually randomised: 226 subjects in the LEO 90105 treatment group, 227 subjects in the Dovonex® treatment group and 223 subjects in the Rinderon®-DP treatment group.

#### Diagnosis and main criteria for inclusion:
Eligible subjects were Japanese patients of either sex, aged 20 years or more, with a clinical diagnosis of psoriasis vulgaris amenable to topical treatment, involving arms and/or trunk and/or legs, a minimum modified psoriasis area and severity index (m-PASI) score for extent of 2 in at least one body region (i.e. psoriasis affecting at least 10% of arms, and/or 10% of trunk, and/or 10% of legs), and a physician’s global assessment of psoriasis on trunk/limbs of mild to very severe. Psoriasis vulgaris on the trunk/limbs (excluding psoriasis on the genitols/skin folds) had to be no more than 30% body surface area (BSA). A target lesion was required to be a minimum of 5 cm at its longest axis, scoring at least 3 for each of redness, thickness and scaliness, and at least 10 in total by the physician’s assessment of severity of the target lesion. Females of childbearing potential had to have a negative pregnancy test result at Day 0 (Visit 1) and had to agree to use an adequate method of birth control during the study.

Test product, dose and mode of administration, batch number:
**Name of Sponsor/Company:** LEO Pharma A/S

**Name of Finished Product:** LEO 90105 ointment

**Name of Active Ingredient:** Calcipotriol hydrate plus betamethasone dipropionate

**Volume:**

**Page:**

**Duration of treatment:**

Up to 4 weeks, with a washout/screening phase of up to 4 weeks and a follow-up phase of 2 weeks

**Reference therapy, dose and mode of administration, batch number:**

Dovonex® ointment (calcipotriol 50 mcg/g) applied topically twice daily, batch numbers: 1109530301 and 1109530302

Rinderon®-DP ointment (betamethasone dipropionate 0.64 mg/g [equivalent to 0.5 mg/g betamethasone]) applied topically once daily, batch number: 1109530401

Vehicle of LEO 90105 ointment (containing no active ingredients) applied topically once daily, batch number: 1109530201

Vehicle of Rinderon®-DP ointment (containing no active ingredients) applied topically once daily, batch number: 1109530501

**Criteria for evaluation:**

**Efficacy:**

The primary efficacy endpoint was the percentage change in m-PASI from baseline to Week 4. The secondary efficacy endpoints were the percentage change in composite severity score for the target lesion from baseline to Week 4, percentage change in m-PASI from baseline to Week 1, and subjects classified as ‘clear’ or ‘almost clear’ by the physician’s global assessment of disease severity at Week 4.

**Safety:**

Safety was assessed based on any reported adverse events (AEs), any reported adverse drug reactions (ADRs), reasons for withdrawal from the study, and changes in laboratory parameters from baseline to Week 4.

**Statistical methods:**

For continuous endpoints, e.g. the change in m-PASI from baseline to Week 4, the treatment groups were compared using analysis of covariance (ANCOVA) including pooled centre, treatment and baseline value in the model. For the binary endpoint, i.e. subjects classified as ‘clear’ or ‘almost clear’ by the physician’s global assessment at Week 4, the treatment groups were compared using the Cochran-Mantel-Haenszel test with adjustment for the effect of pooled centre.

**SUMMARY – CONCLUSIONS**

**EFFICACY RESULTS:**

The primary endpoint, the percentage change in m-PASI from baseline to Week 4 (last observation carried forward [LOCF]), showed that LEO 90105 ointment was statistically significantly superior to both Dovonex® ointment and Rinderon®-DP ointment. The mean value of percentage change in m-PASI from baseline to Week 4 (LOCF) for the full analysis set (FAS) was -64.3 in the LEO 90105 treatment group, compared with -50.5 in the Dovonex® treatment group and -53.6 in the Rinderon®-DP treatment group. LEO 90105 ointment was statistically significantly more effective than Dovonex® ointment (95% CI: -18.1 to -8.2; p<0.0001) and Rinderon®-DP ointment (95% CI: -15.7 to -5.7; p<0.0001). The results for the per protocol analysis set (PPAS) were similar. The secondary endpoints showed that LEO 90105 ointment was statistically significantly superior to both Dovonex® ointment and Rinderon®-DP ointment in the mean value of percentage change in composite severity score of the target lesion from baseline to Week 4 (LOCF), the mean value of percentage change in m-PASI from baseline to Week 1 (LOCF), and the proportion of subjects achieving ‘clear’ or ‘almost clear’ disease according to the physician’s global assessment at Week 4 (LOCF). The mean value of percentage change in composite severity score of the target lesion from baseline to Week 4 (LOCF) was -70.5 in the LEO 90105 treatment group, compared with -57.1 in the Dovonex® treatment group and -58.6 in the Rinderon®-DP treatment group. The mean value of percentage change in m-PASI from baseline to Week 1 (LOCF) was -39.1 in the LEO 90105 treatment group, compared with -23.7 in the Dovonex® treatment group and -29.5 in the Rinderon®-DP treatment group. The proportion of subjects achieving ‘clear’ or ‘almost clear’ disease according to the physician’s global assessment at Week 4 (LOCF) in the LEO 90105 treatment group was 39.4%, compared with 22.9% in the Dovonex® treatment group and 19.3% in the Rinderon®-DP treatment group.

**SAFETY RESULTS:**

Overall 60 AEs were reported in 52 subjects (23.0%) in the LEO 90105 treatment group, compared with 62 AEs reported in 54 subjects (23.9%) in the Dovonex® treatment group and 46 AEs reported in 40 subjects (17.9%) in the Rinderon®-DP treatment group. The most common system organ classes (SOCs) of AEs were ‘infections and infestations’, ‘skin and
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subcutaneous tissue disorders’, ‘injury, poisoning and procedural complications’, and ‘investigations.’ The most common AE was nasopharyngitis, followed by psoriasis, folliculitis, and glucose urine present. The majority of AEs were not considered related to study treatment by the investigators. Overall nine ADRs were reported by nine subjects (4.0%) in the LEO 90105 treatment group, compared with 16 ADRs reported by 15 subjects (6.6%) in the Dovonex® treatment group, and four ADRs reported by four subjects (1.8%) in the Rinderon®-DP treatment group. The most common ADR was psoriasis, which was reported by 0.4%, 3.1%, and 0.9% of subjects in the LEO 90105, Dovonex®, and Rinderon®-DP treatment groups, respectively. No other ADRs were reported by more than two subjects in any treatment group. During the study, one subject died of severe acute coronary syndrome, which was considered by the investigator to be unrelated to study treatment. For randomised subjects, other serious adverse events (SAEs) were reported in two subjects in the LEO 90105 treatment group (injury and calculus urinary), one subject in the Dovonex® treatment group (prostate cancer), and one subject in the Rinderon®-DP treatment group (intestinal obstruction). All of these SAEs were considered to be not related to study treatment by the investigator. AEs led to discontinuation in three subjects in the LEO 90105 treatment group (one death excluded), eight subjects in the Dovonex® treatment group, and one subject in the Rinderon®-DP treatment group. Laboratory abnormalities were reported as AEs for two subjects in the LEO 90105 treatment group and six subjects in the Rinderon®-DP treatment group. These abnormalities were mild and not related to study treatment. The majority of subjects in all treatment groups had laboratory values within the normal reference range at baseline and Week 4.

**CONCLUSION:**

LEO 90105 ointment used once daily is verified to be more effective with a more rapid onset of action than Dovonex® ointment twice daily and also than Rinderon®-DP ointment once daily in Japanese subjects with psoriasis vulgaris. In this study, LEO 90105 ointment was safe over this time. LEO 90105 ointment is therefore considered to be as safe and effective, with the same favourable benefit/risk ratio, in the treatment of Japanese patients with psoriasis as in the overseas patient population.

**Date of the Report:**

29-Jul-2013