**SYNOPSIS**

**Name of Sponsor/Company:** Individual Trial Table Referring to Part of the Dossier

**Name of Finshed Product:**

**Name of Active Ingredient:**
- Calcipotriol
- Calcitriol

**Title of Trial:**
An Irritation study with new calcipotriol ointment formulations in healthy subjects.

**Investigators:**

**Trial centre(s):**
Single centre, France.

**Publication (reference):** Not applicable

**Trial period:** 2 months
- Date of first enrolment: 23-APR-2010
- Date of last completed: 12-May-2010

**Phase of development:** 1

**Objectives:**
The primary objective of this study was to evaluate and compare the skin irritation potential of six different calcipotriol ointment formulations, Daivonex®/Dovonex® cream and Siliks® ointment after repeated applications on intact skin in healthy subjects.
The secondary objective was to assess the safety in terms of incidence and severity of adverse events, adverse drug reactions and reasons for withdrawal from the study.

**Methodology:**
A single centre, investigator blinded, within-subject randomised, active-controlled repeated dose study in healthy subjects.
The study consisted of a screening visit, a treatment period of 10 days, and, if applicable, a follow-up visit. Within 15 days before treatment the screening visit for study eligibility of the subjects took place. During the treatment phase, the six (6) investigational products (6 new calcipotriol ointment formulations) and the two (2) reference products (Daivonex®/Dovonex® cream and Siliks® ointment) were applied on the mid back of each subject on eight (8) test sites under occlusive conditions. A total of 8 patch applications were performed over 10 days (i.e., once daily from Monday to Tuesday the following week, except Sunday). The patches were removed after 24 hours ± 3 hours for patches applied from Monday to Friday and after 48 hours ± 3 hours for patches applied on Saturday.
Clinical assessments of skin reactions were performed for each site at Day 1 (baseline) immediately prior to the first application and 30 to 60 minutes after removal of the patches at the following visits. Transepidermal water loss (TEWL) measurements of each test site were performed at Day 1 (baseline) immediately prior to the first application and 30 to 60 minutes after removal of the patches at Day 5 (visit 6) and Day 10 (visit 10).
During the treatment phase local and systemic adverse events were reported on an ongoing basis. If an adverse event (serious or non-serious), classified as possible or probably related to the study medication or not assessable in relation to the trial medication, was ongoing at the subject’s last on-treatment visit, a follow-up visit/contact was to take place 14 (±2) days after that visit.

**Number of subjects (planned and analysed):**
- 24 subjects were planned, 26 were enrolled and 24 were randomised. The safety and per protocol analysis sets comprised all 24 randomised subjects.
Following verbal and written information about the trial, the subject had to provide signed and dated informed consent before any study related activities were carried out.

Main criteria for inclusion:
1. Males or females of non-child bearing potential
2. Healthy subjects, 18 to 65 years of age
3. Subjects with skin types I to IV according to Fitzpatrick Scale
4. Subjects without erythema on test areas on the mid back skin (visual irritation score = 0) at baseline (Day 1), before randomisation.

Main criteria for exclusion:
1. Females who were pregnant, or who wished to become pregnant during the study, or who were breast feeding
2. Any topical or systemic corticosteroids or immuno-suppressors within 3 weeks prior to randomisation
3. Any other medication which might interfere with the study results, in particular topical drugs applied on the test area within 2 weeks prior to randomisation
4. Any other products which might interfere with the study results, in particular emollients, creams, gels, lotions and body powders applied on the test area within 24 hours prior to randomisation
5. Any systemic or cutaneous disease that might confound interpretation of the study results (e.g., atopic dermatitis, eczema, psoriasis)
6. Scars, moles, sunburn, or other blemishes in the test area which might interfere with grading
7. Exposure to excessive or chronic UV radiation (i.e., sunbathing, solarium, phototherapy) within 2 weeks prior to randomisation or was planned during the study period
8. Known or suspected hypersensitivity to any component of the investigational products

Test product, dose and mode of administration, batch number:
1. Formulation A Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 08-Jun-2010. 2. Formulation B Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 12-Jun-2010. 3. Formulation C Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 15-Jun-2010. 4. Formulation D Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 01-Jun-2010. 5. Formulation E Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 24-Jun-2010. 6. Formulation F Calcipotriol 50 mcg/g ointment, batch number/expiry date: [Redacted] / 23-Jun-2010.

Route of administration and dosage: Topical. Fifty (50) μl per application of each test product on the intact skin on the back.

Duration of treatment:
The treatment phase was 10 days (8 applications).

Reference therapy, dose and mode of administration, batch number:
1. Daivonex®/Devone® cream (calcipotriol 50 mcg/g), batch number/expiry date: [Redacted] / Aug 2011. 2. Silkis® ointment (calcitriol 3mcg/g), batch number/expiry date: [Redacted] / Feb-2012.

Route of administration and dosage: Topical. Fifty (50) μl per application of each test product on the intact skin on the back.

Criteria for evaluation:
Skin Reaction:
The primary response criterion was the cumulative irritation score at Day 10.
The secondary response criterion were 1) Investigators assessment of the Dermal response at each assessment, 2) The cumulative irritation score at Day 5, 3) The number of days until a Dermal Response of 6 or more was recorded, 4) The total number of observations with an irritation score of 6 or more for each product, 5) The change in the TEWL at each assessment compared to baseline.

Safety:
Safety was assessed in terms of incidence and severity of adverse events (AE), adverse drug reactions (ADR) and reasons for withdrawal from the study.

Statistical methods:
The cumulative irritation score at Day 10 was analysed using a mixed effects model with treatment groups and test sites as fixed effects and subjects as random effects. Treatment comparisons were made from the model by t-tests with 5% level of significance. Due to the exploratory nature of the study, no correction for multiplicity was considered necessary. The cumulative irritation score at the end of treatment (Day 10) was tabulated by treatment group showing the mean, SD, minimum and maximum values.

The investigators' assessment of Dermal Response was tabulated by visit for each treatment group presenting the number and percentage of subjects. The cumulative irritation score at Day 5 was tabulated by treatment group showing the mean cumulative irritation score, SD, minimum and maximum values. The change in TEWL from baseline to Day 10 was analysed similarly to the Day 10 cumulative irritation score.

SUMMARY – CONCLUSIONS
SKIN REACTION RESULTS:
Calcipotriol C was the only formulation of the six new calcipotriol ointments that had a lower cumulative irritation score than the reference products after 10 days of treatment (the difference was not statistically significant). The mean cumulative irritation score was 0.67, 0.66, 0.61, 1.03, 1.06, 1.13, 0.59 and 0.56 for Calcipotriol A to F ointments, calcipotriol cream (Daivonex® cream) and calcitriol (Silkis® ointment), respectively.

After 5 days of treatment the mean cumulative irritation score was 0.60, 0.59, 0.53, 0.81, 0.96, 1.01, 0.65 and 0.50 for Calcipotriol A to F ointments, calcipotriol cream (Daivonex® cream) and calcitriol (Silkis® ointment), respectively. No Dermal Response scores greater than 3 were recorded for any subject in the study.

The mean change from baseline to end of treatment (Day 10) in TEWL was 4.89, 2.66, 4.31, 5.36, 6.17, 8.88, 5.83 and 3.33 g/m²/hour for Calcipotriol A to F ointments, calcipotriol cream (Daivonex® cream) and calcitriol (Silkis® ointment), respectively.

SAFETY RESULTS:
There were no ADRs, no withdrawals due to AEs or serious adverse events in the study.

CONCLUSION:
Calcipotriol C ointment appeared to be less irritant on skin than the other investigational products after 10 days of treatment.

The treatments were well tolerated.

Date of the Report:
07-Dec-2010