SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S
Name of Finished Product: TACLONEX
Name of Active Ingredient: Calcipotriene plus betamethasone dipropionate

Title of trial: Safety and efficacy of TACLONEX ointment in adolescent patients (aged 12 to 17 years) with psoriasis vulgaris

Trial centres: Seven centres in the US
Publication (reference): Not applicable

Trial period (years) (date of first enrolment) 15-JUL-2009 (date of last completed) 05-DEC-2011 Phase of development: 2

Objectives:
The primary objective was to evaluate the safety of TACLONEX ointment in the treatment of psoriasis vulgaris on the trunk and/or limbs in adolescent patients (aged 12 to 17 years).
The secondary objective was to evaluate the efficacy of TACLONEX ointment in the treatment of psoriasis vulgaris on the trunk and/or limbs in adolescent patients (aged 12 to 17 years).

Methodology:
A national, multi-centre, prospective, non-controlled, single-group, 4-week study in psoriatic adolescents. The study consisted of a washout/screening phase, a treatment phase and, if needed, a follow-up phase. The wash-out/screening phase lasted for 3 days to 6 weeks, depending on the prior use of excluded treatments, with two visits (screening visit (SV) 1 and 2). The treatment phase lasted for 4 weeks, with visits 1-3. The follow-up phase lasted for up to 4 weeks, depending on whether the subject had adrenal suppression or ongoing adverse drug reactions (ADRs) at the end of treatment. All subjects received TACLONEX ointment to apply once daily to psoriasis vulgaris on the trunk/limbs in the evening for 4 weeks. Before treatment start and after 4 weeks treatment ACTH-challenge test, hematology, biochemistry, urinalysis, physical examination and measurement of blood pressure/heart rate were performed. Adverse events (AEs) were recorded at all visits after the first visit. At weeks 0, 2 and 4 in the treatment phase, the investigator and subject each made a global assessment of disease severity. The investigator also assessed the extent and severity of clinical signs of psoriasis by body region.

Number of subjects (planned and analysed): Thirty subjects were planned and 33 subjects were treated. All 33 were in the full and safety analysis sets, and 32 in the per protocol analysis set.

Diagnosis and main criteria for inclusion:

Main criteria for inclusion:
- Aged 12 to 17 years, inclusive.
- Attending a hospital out-patient clinic or the private practice of a dermatologist for treatment of psoriasis. For those attending the private practice of a dermatologist, the centre had to have experience of performing the ACTH-challenge test, and the ability/facilities to deal with allergic/anaphylactic reactions. The centre should also have close proximity, and easy access, to an acute general hospital.
- At visit 1, a clinical diagnosis of psoriasis vulgaris on the trunk and/or limbs which was:
  - amenable to topical treatment with a maximum of 60 g of study medication per week, and
  - of an extent of 5-30% of BSA (any psoriasis on the genitals or skin folds should not be included in this calculation of...
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Main criteria for exclusion:
- A history of serious allergy, serious asthma, or serious allergic skin rash.
- A history of sensitivity to any medication (including ACTH/tetracosactide/cosyntropin), or to any component of CORTROSYN™ or TACLONEX ointment.
- PUVA or Grenz ray therapy within 4 weeks prior to Visit 1 and during the study.
- UVB therapy within 2 weeks prior to Visit 1 and during the study.
- Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris within the following time period prior to Visit 1 (or enrolment) and during the study:
  - etanercept - within 4 weeks prior to Visit 1
  - adalimumab, alefacept, efalizumab, infliximab - within 2 months prior to Visit 1
  - ustekinumab - within 4 months prior to Visit 1
  - experimental products - within 4 weeks/5 half-lives (whichever is longer) prior to enrolment
- Systemic treatment with corticosteroids (including inhaled and nasal) within 12 weeks prior to SV2 and during the study.
- Any topical treatment for any disease on any body location with Class 1 to 5 corticosteroids within 2 weeks prior to SV2, with Class 6 or 7 corticosteroids or vitamin D analogues within 1 week prior to SV2, or during the study. In addition, for psoriasis of the trunk/limbs (excluding psoriasis of the genitals/skin folds), no other treatments (such as dithranol and tar) were allowed within 2 weeks prior to visit 1, except for emollient which could be used up to, but not after, visit 1.
- Treatment with any of the following medications within 4 weeks prior to SV2 or during the study: enzymatic inducers (e.g., barbiturates, phenytoin, rifampicin, carbamazepine), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole), hypoglycemic sulfonamides, antidepressive medications, estrogen therapy or any other medication known to affect cortisol levels or HPA-axis integrity.
- Treatment with any non-marketed drug substance (i.e., an agent which had not yet been made available for clinical use following registration) within 4 weeks prior to enrolment, or longer if the class of substance met any of the above criteria for a longer washout (e.g., biological treatments).
- Calcium supplements or vitamin D supplements within 4 weeks prior to SV2 and during the study.
- Planned initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (e.g., beta-blockers, anti-malaria drugs, lithium, ACE inhibitors) after visit 1.
- Planned excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sun lamps, etc) after visit 1.
- Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
- Any of the following conditions present on the area(s) to be treated with study medication: viral (e.g., herpes or varicella) lesions of the skin, fungal or bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, acne rosacea, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, ulcers or wounds.
- Other inflammatory skin diseases that could confound the evaluation of psoriasis vulgaris of the trunk and/or limbs.
- Any of the following conditions if known or suspected: severe renal insufficiency, severe hepatic disorders, disorders of calcium metabolism associated with hypercalcemia, any cardiac condition or an endocrine disorder that could affect the results of the ACTH challenge test.
- Diabetes mellitus
- Clinical signs or symptoms of Cushing’s disease or Addison’s disease.
- Any clinically significant abnormality in the laboratory tests, physical examination or blood pressure/heart rate...
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**Test product, dose and mode of administration, batch number:**
TACLONEX ointment (calcipotriene 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate)) applied topically once daily up to 60 g ointment per week. Batch numbers /expiry dates: 08089661/ 02.2010; 092787101/ 09.2011; 110547101/ 02.2013.

**Duration of treatment:**
4 weeks

**Reference therapy, dose and mode of administration, batch number:**
Not applicable

**Criteria for evaluation:**

### Safety:

**Primary response criteria:**
- ADRs
- Serum cortisol concentration of ≤18 mcg/dL at 30 minutes after ACTH-challenge at end of treatment.
- Serum cortisol concentration of ≤18 mcg/dL at 30 and 60 minutes after ACTH-challenge at end of treatment.
- Change in albumin-corrected serum calcium from baseline to end of treatment.
- Change in urinary calcium:creatinine ratio from baseline to end of treatment.

**Secondary response criteria:**
- AEs
- Change in other laboratory parameters from baseline to end of treatment.
- Reasons for withdrawal
- Change in blood pressure and heart rate from baseline to end of treatment.

### Clinical Efficacy:

**Secondary response criteria:**
- ‘Controlled disease’ (‘clear’ or ‘almost clear’) by the investigator’s global assessment of disease severity at week 4.
- ‘Controlled disease’ (‘clear’ or ‘very mild’) by the patient’s global assessment of disease severity at week 4.
- The change in modified psoriasis area and severity index (modified PASI) from baseline to week 4.
- Modified PASI 75 (at least 75% reduction in modified PASI) and modified PASI 50 (at least 50% reduction in modified PASI) at week 4.

**Statistical methods:**
No formal sample size calculation was performed, but the upper limit of an exact two-sided 95% confidence interval for the probability of observing a specific AE, when 0 out of 30 possible events have been observed, is 12% assuming a binomial distribution.

The following were presented with a 95% confidence interval:
- Mean change in albumin-corrected serum calcium, PTH, serum phosphorus and urinary calcium:creatinine and phosphorus:creatinine ratios from baseline to week 4.
- The percentage of subjects who achieved ‘controlled disease’ by investigator’s global assessment of disease severity at week 4.
- The percentage of subjects who achieved ‘controlled disease’ by patient’s global assessment of disease severity at week 4.
- The mean percentage change in modified PASI from baseline to week 4.
- The percentage of subjects with modified PASI 75 and modified PASI 50 at week 4.

**SUMMARY - CONCLUSIONS**

**SAFETY:**
None of the subjects had a serum cortisol concentration of ≤18 mcg/dL at either 30 or 60 minutes following ACTH challenge at end of treatment. There were no clinically significant mean changes in albumin-corrected serum calcium or urinary calcium:creatinine ratio. No albumin-corrected serum calcium values above the upper reference limit were reported. One subject had an increase from a normal urinary calcium:creatinine ratio at baseline to a value above the upper reference limit at week 4. There were no individual clinically significant abnormalities in the biochemistry or haematology parameters.
A total of 16 AEs were experienced by 11 (33.3%) subjects. The most commonly affected SOCs of the AEs were ‘Infections and infestations’ and ‘Nervous system disorders’ with four subjects each. Two of the AEs were ADRs (headache and pruritus), both of mild intensity. There were no serious adverse events (SAEs) or withdrawals due to AEs in the study.

### CLINICAL EFFICACY:
At week 4, 61% of subjects had ‘controlled disease’ by investigator’s global assessment. The mean percentage reduction in modified PASI from baseline to week 4 was 72.5% (95% CI: 81.1 to 63.9%). The proportion of subjects with modified PASI 75 and PASI 50 at week 4 was 52% and 85%, respectively. There were 70% of subjects with ‘controlled disease’ at week 4 by patient’s global assessment.

### CONCLUSIONS:
There was no evidence of adrenal suppression following study treatment. There were no clinically significant mean changes in albumin-corrected serum calcium or urinary calcium:creatinine ratio, and no cases of hypercalcaemia were reported. One subject had an increase in urinary calcium:creatinine ratio, and a relationship to study treatment cannot be excluded. TACLONEX ointment was well tolerated with few ADRs, no SAEs and no withdrawals.

The efficacy level in the study suggests that TACLONEX ointment is effective in the treatment of psoriasis vulgaris in adolescents.

In conclusion, in this small, non-controlled study TACLONEX ointment appeared to be safe and effective in the treatment of psoriasis vulgaris in adolescents.

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