CLINICAL STUDY REPORT SYNOPSIS

Sponsor
LEO Pharmaceutical Products Ltd. A/S

Investigational Product
Xamiol® Gel

Title of the Study
Multicentre, Randomized, Investigator-Blinded, Parallel-group Study to Assess the Efficacy and Safety of Xamiol® Gel Compared to Calcipotriol Scalp Solution in Patients with Scalp Psoriasis

Study Time Period
The first subject was enrolled on 17th Sep 2010, and the last subject completed the study on 01st Mar, 2011

Study Objective
Primary
To compare the efficacy of once daily treatment for 4 weeks of Xamiol® gel (combination of Calcipotriol plus betamethasone dipropionate) with twice daily treatment of Calcipotriol Scalp Solution in patients with scalp psoriasis.

Secondary
To observe the safety of Xamiol® gel in patients with scalp psoriasis.

Study Design
A multicentre, prospective, randomized, investigator-blinded, 2-arm, parallel group, 4-week study in patients with scalp psoriasis. Patients were treated once daily for up to 4 weeks with Xamiol® gel (Calcipotriol 50 mcg/g plus betamethasone dipropionate 0.5 mg/g) or twice daily for up to 4 weeks with Calcipotriol Scalp Solution. Randomisation to treatment arms was with a 1:1 ratio.

Subjects Number
240 subjects planned. A total of 244 subjects were randomized.

Subjects Selection
Inclusion criteria:
1. Patients of either gender between 18 and 65 years of age (both inclusive).
2. At visit SV2 and visit 1, a clinical diagnosis of scalp psoriasis which was:
   - of an investigator’s assessment of clinical signs of the scalp at least ≥ 2 in one of the clinical signs, redness, thickness and scaliness, and at least 1 in each of the other two clinical signs, and total score ≥ 4
   - of an extent of 10% or more of the total scalp area
- of at least moderate severity according the investigator’s global assessment

3. Clinical signs of psoriasis vulgaris on trunk and/or limbs (involving a maximum of 10% Body Surface Area), or earlier diagnosed with psoriasis vulgaris on trunk and/or limbs.

4. The patient has provided signed and dated informed consent before any study related activity is carried out.

5. For patients from the Centre at [redacted]: patients with morning serum cortisol and plasma ACTH within the normal ranges at visit SV2.

6. Female of childbearing potential using a reliable method of contraception for at least 1 month before the study start and during the course of the study (e.g., oral contraceptive pill, intrauterine device, contraceptive patches, implantable contraception, condoms) or females of non-childbearing potential (i.e. postmenopausal (absence of menstrual bleeding for 2 years), hysterectomy, bilateral ovariectomy or tubal section/ligation). For patients in the Centre at [redacted]: Oestrogen based hormonal contraceptives were not allowed.

**Exclusion criteria:**

1. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.

2. Patients with any of the following conditions present on the scalp area: viral lesions, fungal and bacterial skin infections, parasitic infections, skin manifestations in relation to syphilis or tuberculosis, rosacea, acne vulgaris, acne rosacea, atrophic skin, striae atrophicae, fragility of skin veins, ichthyosis, ulcers and wounds.

3. Any other inflammatory skin diseases that may confound the evaluation of scalp psoriasis.

4. Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on scalp psoriasis (e.g., alefacept, efalizumab, etanercept, infliximab) within 3 months prior to visit 1 and during the study.

5. Systemic treatment with all other therapies than biologicals, with a possible effect on scalp psoriasis (e.g., corticosteroids, vitamin D analogues, retinoids, immunosuppressants) within 4 weeks prior to SV2 or during the study.

6. PUVA therapy within 4 weeks prior to randomisation (visit 1) or during the study.

7. UVB therapy within 2 weeks prior to randomisation (visit 1) or during the study.

8. Therapies within 2 weeks prior to SV2 and during the study:
   a) Topical treatment of psoriasis with potent or very potent (WHO group III or IV) corticosteroids. WHO I and II topical steroid (e.g., hydrocortisone
butyrate, desonide) were allowed during the study on non-scalp psoriasis lesions,
b) Topical treatment with immunomodulator, e.g. Tacrolimus,
c) Topical treatment with vitamin D analogues (e.g., Calcipotriol, tacalcitol, calcitriol),
d) Any topical treatment of the scalp (except for non-steroid medicated shampoos and emollients),
e) Other types of psoriasis treatment, e.g. Chinese medicine, processed Chinese medicine, or hot spring, etc.
9. Planned initiation of, or changes to concomitant medication that could affect scalp psoriasis (e.g., beta blockers, anti-malaria drugs, lithium) during the study.
10. Known or suspected hypersensitivity to component(s) of the Investigational Products.
11. Known or suspected abnormality of the calcium homeostasis.
12. Known or suspected renal insufficiency or hepatic disorders (ALT and/or AST > 2 times the UNL and/or abnormal serum creatinin), or severe heart disease.
13. Clinical signs or symptoms of Cushing’s disease or Addison’s disease.
14. Planned excessive exposure to sun (e.g. when working outdoors) during the study, which may affect scalp psoriasis.
15. Females who were pregnant, or of child-bearing potential and wished to become pregnant during the study, or who were breast-feeding.
16. Females of child-bearing potential with a positive serum or urine pregnancy test at SV2.
17. Any clinically significant abnormality following review of screening laboratory tests (blood and urine samples), physical examination or blood pressure/heart rate measurement performed at SV2.
18. Participation in any other interventional clinical trial within 4 weeks prior to randomisation.
19. Patients who had known or suspected poor compliance or who can not complete the clinical trial, such as patients with alcoholism, drug dependence or mental disease, and patients the researchers have judged not suitable for participating the clinical trial of the test drug.
For the Centre at: [redacted]
20. Systemic treatment with corticosteroids (including inhaled and nasal) within 12 weeks prior to SV2 or during the study.
21. Planned initiation of, or changes to ongoing topical treatment of psoriasis on the trunk/limbs and on the face and/or genital/skin folds with topical corticosteroids during the study.
22. Oestrogen therapy (including contraceptives) or any other medication known
to affect cortisol levels / HPA axis function within 4 weeks prior to SV2 or during the study.

23. Cytochrome P450 3A4 inducers (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the study.

24. Systemic or topical cytochrome P450 3A4 inhibitors (e.g., ketoconazole) within 4 weeks prior to SV2 or during the study.

25. Hypoglycemic sulfonamides within 4 weeks prior to SV2 or during the study.

26. Antidepressive medications within 4 weeks prior to SV2 or during the study.

27. Known or suspected endocrine disorder that may affect the the HPA axis function.

28. Patients with diabetes mellitus.

29. Irregular sleep schedules. Not following nocturnal sleep patterns.

The Study Drugs

Investigational drug:
Xamiol® gel (LEO Pharmaceutical Products Ltd. A/S, Batch No. 091177301, 0914230201): Calcipotriol (as hydrate) 50mcg/g plus betamethasone 0.5mg/g (dipropionate), 30g/bottle
The Investigational Product was used once daily for 4 weeks for topical treatment of scalp psoriasis, with weekly maximum application on scalp lesions being less than 100g.

Comparator:
Calcipotriol Scalp Solution (LEO Pharmaceutical Products Ltd. A/S, Batch No. 091177401): Calcipotriol (as hydrate) 50 mcg/ml, 30ml/bottle.
The Reference Product was used twice daily for 4 weeks for topical treatment of scalp psoriasis, with weekly maximum usage being less than 60ml.

Efficacy Evaluation

Primary endpoints:
Patients with “Controlled disease” in terms of “Clear” or “Minimal” according to investigator’s global assessment of disease severity at week 4.

Secondary endpoints:
1. Patients with “Controlled disease” in terms of “Clear” or “Minimal” according to investigator’s global assessment of disease severity at week 2.
2. Patients with “controlled disease” in term of “Clear” or “Very mild” according to patient’s global assessment of disease severity at week 2 and 4.
3. Patients with success (Total sign score = 0 or 1) at week 4.
4. For each clinical sign (redness, thickness, scaliness), the percentage of patients with success (clinical score = 0) at week 4.
5. Patients with success (Patient’s itching score = none ) at week 4.
6. Evaluation of the quality of life: Change in quality of life from baseline to
week 2 and 4 by use of Dermatology Life Quality Index (DLQI).

**Safety Evaluation**
- Any reported adverse event
- Any reported adverse drug reaction
- Reasons for withdrawal
- Clinical significant laboratory abnormalities from baseline to week 4.
- Changes in the morning serum cortisol and plasma ACTH from baseline to week 4 on a subset group of patients (xxxx xxxxxx xx xxxxxxxx xxxxxxx)
Primary efficacy evaluation:
The Full Analysis Set (FAS) and Per Protocol Set (PPS) population were used for primary efficacy evaluation. The analysis for the FAS was the primary whereas the analysis for the PPS served as supportive purposes. The proportion of patients who achieved “Controlled disease” according to the investigator’s global assessment of disease severity at week 4 was compared between the treatment groups using the Cochran-Mantel-Haenszel test adjusting for the effect of centre (The Breslow-Day test for homogeneity of the odds ratio across centres was calculated.). The odds ratio (odds of “Controlled disease” of Xamiol® gel relative to that of Calcipotriol scalp solution), its 95% confidence interval and P-value were calculated. If the 95% CI of OR was greater than 1, the superiority of study group would be established as compared to control group. The disease severity and “Controlled disease” according to the investigator’s global assessment of disease severity were described for all subjects and by centre during the study.

Safety analysis of adverse events:
The incidence of adverse events (AEs) was tabulated according to the version 13.1 of the MedDRA dictionary and was summarized by System Organ Class (SOC) and preferred term. The number and percentage of patients experiencing each type of adverse event (according to MeDRA Preferred Terms and System Organ Class) was tabulated by treatment group regardless of the number of times each adverse event was reported by each patient. Chi-square tests were used to compare the proportion of patients with AEs and adverse drug reactions (ADR) between treatment groups. Listings of AEs, ADRs, Significant AE and SAEs are provided.

Estimated sample size:
The calculation of sample size was based on the Chi-square test, by assuming 50% and 20% efficacy rates in Xamiol® gel group and Calcipotriol scalp solution control group, respectively, after 4 weeks of treatment. According to this calculation, at 5% significance level, when each group had 50 trial subjects, the study would have 89.4% power to detect the between-group difference. At the same 5% significance level, when each group has 100 subjects, the power would reach 99.6%. When each group enrolled over 120 subjects, the power would exceed 99.9%.

Patients in the Centre at [redacted] were assessed for morning serum cortisol and plasma ACTH at baseline and at end of treatment (week 4). At least 40 evaluable patients were planned to be enrolled in the [redacted]. So the study was planned to provide
assessments of the changes in the morning serum cortisol and plasma ACTH from baseline to the end of treatment (week 4) for at least 20 patients in each group. If more than 40 patients were enrolled at this centre, they would also provide morning serum cortisol and plasma ACTH at baseline and at end of treatment.

Results

General information:
The date of the first enrollement in the trial was on 17 September 2010 and the date of the last patient out was on 01 March 2011. The study period was about seven months. A total of 9 centers in China participated in the study, with a total of 244 randomised patients, 120 patients to Xamiol® gel and 124 patients to Calcipotriol scalp solution, and all were included in the full analysis set. There were 242 subjects who were included in the safety analysis set (118 patients to Xamiol® gel group and 124 patients to Calcipotriol scalp solution group). 226 subjects were included in the per protocol analysis set (112 patients to Xamiol® gel group and 114 patients to Calcipotriol scalp solution group). In the center of xxxxxxxx xxxxxxxxxx xxxxxxxx xxxxxxxx, 40 patients were randomised and 37 subjects were included in HPA axis analysis set (18 patients to Xamiol® gel group patients and 19 to Calcipotriol scalp solution group).

The mean age was similar in both groups and was 39.87 years (range: 19.0-65.0 years) in Xamiol® gel group and 38.73 years in Calcipotriol scalp solution group (range: 20.0-64.0 years). There were 73 (60.8%) male subjects in the Xamiol® gel group and 69 (55.6%) male subjects in Calcipotriol scalp solution group. The average duration of psoriasis was similar in both groups, and was 7.43 years in the Xamiol® gel group and 7.50 years in Calcipotriol scalp solution group. For the psoriasis on trunk and limbs, the average body surface area percentage involved with skin lesions according to investigator’s assessment was 3.25% in the Xamiol® gel group and 3.53% in control group; while for the psoriasis on scalp, the average percentage of the scalp area involved with skin lesions according to investigator’s assessment was 54.07% in the Xamiol® gel group and 48.64% in Calcipotriol scalp solution group.

Efficacy results:

· Primary efficacy endpoint
In the full analysis set (FAS): The percentage of subjects with “controlled disease” in terms of “Clear or Minimal” according to investigator’s global assessment of disease severity at week 4 was statistically significantly higher in Xamiol® gel group than in Calcipotriol scalp solution group (87.5% vs. 50.8%) (OR 6.6101, 95% CI 3.4796 to 12.5572, \( P<0.0001 \)). The Breslow-Day test to investigate the consistency of the response across centers was not statistically significant at week 4 indicating no treatment-by-center interactions were found to have an impact on efficacy results (\( P=0.5344 \)). The results of the per protocol set
Secondary efficacy endpoints
For all secondary efficacy endpoints, Xamiol® gel group was superior to Calcipotriol scalp solution group.
At week 2, the rate of subjects with “controlled disease” (with LOCF) according to investigator’s global assessment of disease severity in the Xamiol® gel group was 80.85% versus 25.8% in Calcipotriol scalp solution group, P<0.0001.
At weeks 2 and 4, the rate of controlled disease according to patient’s global assessment of disease severity in the Xamiol® gel group was 79.2% and 90.8%, respectively, in the Xamiol® gel group, versus 37.1% and 60.5% in Calcipotriol scalp solution group, with statistically significant difference between the two groups, at both timepoints, P<0.0001.
At the end of the treatment (week 4), the percentage of patients with success (Total Sign Score ≤ 1) was 64.2% in the Xamiol® gel group versus 25.8% in Calcipotriol scalp solution group, P <0.0001.
At the end of treatment (week 4), the success rate of each individual clinical sign (redness, thickness and scaliness) was 39.2%, 82.5% and 65.0% in Xamiol® gel group versus 21.0%, 41.1% and 21.8% in Calcipotriol scalp solution group, respectively, with statistically significant difference between the two groups for each of the signs. At the end of treatment (week 4), the success rate of itching was 67.5% in test group versus 38.7% in the control group, respectively, with a statistically significant difference detected between the two groups.
• Quality of Life:
The results of Quality of Life Questionnaire showed improvements from baseline in both groups. There was no statistically significant difference between the two groups in the changes from baseline of the DLQI total score at week 4, while the difference was statistically significant in favour of Xamiol® at week 2. The differences from baseline showed a statistical difference in favour of Xamiol® for the subscale “Daily activities” at week 2 and for the subscale symptoms and feelings” at weeks 2 and 4.

Safety results:
The incidence of AEs was 32.2% in Xamiol® gel group versus 40.3% in Calcipotriol Scalp Solution group, respectively, with no statistical significance. The incidence of adverse drug reactions reported during treatment with Xamiol® gel was lower than with Calcipotriol scalp solution (18.6%, versus 33.1%, respectively P=0.0106). One (1) subject from Xamiol® gel group and two (2) subjects from Calcipotriol Scalp Solution group withdrew from treatment due to ADRs.
The most common clinical ADRs in Xamiol® gel group were skin discomfort
from the scalp lesions at the site application (including pain, warmth, pruritus, paraesthesia) with the incidence being 4.2% (5/118). The same incidence of ADRs including the upper respiratory tract infections was observed (4.2% (5/118). The incidence of ADRs including the skin and subcutaneous tissue disorders (erythema, dermatitis, pruritus, etc.), was 3.4% (4/118), and dizziness 2.5% (3/118).

The most common clinical ADRs in Calcipotriol Scalp Solution group was skin discomfort from the scalp lesions topically treated, including burning pain associated with the area of skin lesions, with the incidence being 25.0% (31/124); followed by skin and subcutaneous tissue lesions (including erythema, dermatitis, etc.), with the incidence rate being 7.3% (9/124); as well as upper respiratory tract infections 1.6%(2/124).

There were 6 subjects respectively in both groups with abnormal laboratory values, which have been reported as possibly related to study drug with the incidence rate respectively being 5.1% in Xamiol® gel group and 4.8% in Calcipotriol Scalp Solution group, which was reflected as abnormal blood urine routine and liver transaminases elevation. There were 2 subjects (one in each of Xamiol® gel group and Calcipotriol Scalp Solution group, respectively) with slight transitory morning serum cortisol decrease, but recovered to normal after 2 weeks.

ADRs in both two study groups were mainly presented with mild severity, or moderate severity, while no ADRs with severe degree had ever occurred. From 22 subjects with ADRs in Xamiol® gel group, 19 subjects were of in mild severity and 3 subjects of moderate severity, compared to 41 subjects with ADRs in Calcipotriol Scalp Solution group, in which 27 subjects were of mild severity and 14 subjects of moderate severity.

HPA test was performed at principal study center, XXXXXXX XXXXXXX XXXXXXXX, with 40 subjects being enrolled; in which 37 subjects entered HPA axis analysis set. The results showed that no subjects were reported with changes of morning plasma adrenocorticotropic hormone (ACTH) when compared the pre-treatment level with the post-treatment level. 6 patients whose morning serum cortisol levels experienced a slight change when compared pre-treatment level to a post-treatment level, in which serum cortisol elevation occurred in 4 subjects (3 in Xamiol® group, 1 in Calcipotriol Scalp Solution group) and slight serum cortisol decrease in 2 subjects (1 in each of groups), the latter was related to the study drug by the investigator's judgement. However, the decreased cortisol levels in the two patients returned to normal 14 days after the study completion.

There were two cases of serious adverse events, the 5th toe comminuted fracture and ovarian neoplasm surgery, respectively, which were not related to study drug by investigator's judgement.
Conclusion

In treating scalp psoriasis, the efficacy of Xamiol® gel was superior to Calcipotriol scalp solution, with a statistically significant difference detected between the two study drugs. The incidence rates of AEs in Xamiol® gel group were lower than in the Calcipotriol scalp solution group but it was not statistically different. The incidence rates of ADRs in the Xamiol® gel group were lower than those in the Calcipotriol scalp solution control group, which was statistically significant. There was no clinically significant impact on the HPA axis from Xamiol® gel in patients with scalp psoriasis after topically treated for 4 weeks as shown by comparison with morning serum cortisol and plasma ACTH in patients before the treatment and after the treatment.

Report Date

June-22-2011