Clinical Study Report Synopsis

Calcipotriol Plus Hydrocortisone Ointment Compared with Tacalcitol Ointment in Patients with Psoriasis Vulgaris on the Face and on the Intertriginous Areas

A phase 3 study comparing an ointment containing calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g with tacalcitol 4 mcg/g ointment and the ointment vehicle alone, all applied once daily in the treatment of psoriasis vulgaris on the face and on the intertriginous areas

An international, multi-centre, prospective, randomised, investigator-blinded, active- and vehicle-controlled, 3-arm, parallel group, 8-week clinical study followed by an observation period of 8 weeks

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development

LEO 80190-O22
23-Oct-2009
2007-003365-41

1 CLINICAL STUDY REPORT SYNOPSIS APPROVAL

1.1 APPROVAL STATEMENT

On behalf of LEO, only the Director, International Clinical Development, LEO and the Head of Biostatistics, LEO HQ are authorised to approve the Clinical Study Report Synopsis.

All LEO approvers will be identified on a signature page of the pdf-file of the final Clinical Study Report Synopsis when the last LEO approval is obtained. The time and date of their e-signatures are likewise presented on the approval page.

The following persons have approved this Clinical Study Report Synopsis using electronic signatures:

[redacted] iostatistics, LEO HQ

[redacted], International Clinical Development, LEO

1.2 APPROVAL STATEMENT INVESTIGATORS

On behalf of all investigators, the International Co-ordinating Investigator approves the Clinical Study Report Synopsis. The International Co-ordinating Investigator approves the Clinical Study Report Synopsis by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this document.

The following person has approved this Clinical Study Report Synopsis

[redacted] MD
International Co-ordinating Investigator

2 SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities Volume: Page:	
Name of Investigational Product/ Finished Product, if available: LEO 80190-O22		
Name of Active Substance: Calcipotriol and hydrocortisone Ointment		

Title of study/ Protocol code number:
Calcipotriol Plus Hydrocortisone Ointment Compared with Tacalcitol Ointment in Patients with Psoriasis Vulgaris on the Face and on the Intertriginous Areas/LEO 80190-O22.

International Co-ordinating Investigator:
[redacted], MD, [redacted] United Kingdom

Trial sites:
Multicentre study conducted at 79 centres (Canada 27 centres, France 25 centres and United Kingdom 27 centres)

Publication (reference):
To be decided

Studied period:	Phase of development:
First subject first visit: 05-MAR-2008 Last subject completed treatment: 14-APR-2009	III

Objectives:
The primary objective was to compare the efficacy and safety of once daily treatment for up to 8 weeks of an ointment containing calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g (hereafter referred to as LEO 80190 ointment) with tacalcitol 4 mcg/g ointment and the LEO 80190 ointment vehicle alone in subjects with psoriasis vulgaris on the face and on the intertriginous areas. Secondary objectives were to investigate the occurrence of and time to relapse and occurrence of rebound after end of treatment in subjects with 'controlled disease' and to obtain data on the quality of life (QoL) of subjects treated with: LEO 80190 ointment, tacalcitol 4 mcg/g ointment and the LEO 80190 ointment vehicle alone.

Methodology:
An international, multi-centre, prospective, randomised, investigator-blinded, active- and vehicle controlled, 3-arm, parallel group, 8-week study, followed by an observation period of 8 weeks, in subjects with psoriasis vulgaris on the face and on the intertriginous areas. Subjects were stratified according to whether they had psoriasis of at least mild severity according to the investigator's global assessment of disease severity (IGA) of the intertriginous areas or not and then randomised in a 3:3:1 ratio to receive once daily treatment for up to 8 weeks with either 1) LEO 80190 ointment or 2) tacalcitol 4 mcg/g ointment or 3) LEO 80190 ointment vehicle. Prior to randomisation (Visit 1) a washout period of up to 4 weeks was to be completed if the subject received anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria. On-treatment visits were performed at

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baseline (Visit 1) and after 1, 2, 4, 6 and 8 weeks (Visits 2-6). A follow-up visit took place 14 days after the subject's last on-treatment visit if a treatment related adverse event (possible, probable or not assessable relationship to study medication) was ongoing. The initial 8 week study period was followed by a treatment free observation period of up to 8 weeks for subjects with 'controlled disease' according to the IGA of the face and/or the intertriginous areas at Week 8. During the observation period, visits took place at 10, 12 and 16 weeks (Visits 7-9) but an extra visit could be conducted between scheduled visits if a subject experienced a worsening of psoriasis on the face and/or the intertriginous areas and treatment needed reinitiating. Efficacy assessments including the IGA, patient's global assessment of disease severity and the investigator's assessment of clinical signs (redness, thickness and scaliness) were performed at all visits during the treatment period (Visits 1-6) for the face and intertriginous areas separately. The IGA was also assessed during the observation period (Visits 7-9). Safety assessments were performed at all post randomisation visits (Visits 2 to 9).

Number of subjects enrolled:

A total of 735 subjects were planned (LEO 80190 ointment group: 315; tacalcitol ointment group: 315; ointment vehicle group: 105). A total of 782 subjects were enrolled and 741 were randomised (LEO 80190 ointment group: 322; tacalcitol ointment group: 317; ointment vehicle group: 102).

Diagnosis and main criteria for eligibility:

Hospital out-patients or patients attending the private practice of a dermatologist or general practitioner experienced in treating psoriasis vulgaris, aged 18 years or above, with signs of, or an earlier diagnosis of, psoriasis vulgaris on the trunk and/or limbs and a clinical diagnosis of psoriasis vulgaris involving the face with an extent of at least 10 cm^2 (the sum of all facial lesions) and a disease severity of at least mild according to the IGA of the face. The treatment areas (the face and the intertriginous areas) must be amenable to topical treatment with a maximum of 10 g of ointment per day and informed consent given. Anti-psoriatic treatments (systemic and topical), light therapy or sun exposure or initiation of other treatments that could affect the course of the disease (e.g. beta-blockers, anti-malarials, ACE inhibitors, vitamin D derivatives) on the areas to be treated were not permitted during the study or within a specified time of study start. Subjects with erythrodermic, exfoliative, guttate or pustular psoriasis, other skin diseases or known or suspected to have severe renal insufficiency, severe hepatic disorders or disorders of calcium metabolism were excluded.

Investigational product, dose , method of administration, lot numbers:

LEO 80190 ointment: Calcipotriol 25 mcg/g (as hydrate) plus hydrocortisone 10 mg/g ointment applied topically once daily on affected areas on the face and intertriginous areas.

Lot numbers: 0731661, 0821761

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Reference product, dose , method of administration, lot numbers:

Tacalcitol 4 mcg/g (as mono-hydrate) ointment. Lot numbers: 0640712, 0716821, 0718834, 0733851, 0739871, 0806922, 0816942, 0816951

LEO 80190 ointment vehicle. Lot numbers: 0731662, 0819163

Both applied topically once daily on affected areas on the face and intertriginous areas.

Duration of treatment:

A treatment period of up to 8 weeks followed by a treatment free observation period of up to 8 weeks.

Criteria for evaluation

Efficacy :

Primary response criterion: Subjects with 'controlled disease' according to the IGA of the face at Week 8. 'Controlled disease' of the face was defined as clear or almost clear according to the IGA of the face for subjects with a baseline (Visit 1) severity of moderate or worse and clear according to the IGA of the face for subjects with a baseline (Visit 1) severity of mild.

Secondary response criteria:

'Controlled disease' according to the IGA of the face at Week 4.

'Success' according to Total Sign Score (TSS) of the face (scores 0 or 1) at Week 8.

'Controlled disease' according to the IGA of the intertriginous areas at Week 8.

'Success' according to TSS of the intertriginous areas (scores 0 or 1) at Week 8.

Subjects with relapse during the study and time to relapse.

Subjects with rebound during the study.

Prior to unblinding the secondary response criteria 'Success' according to the severity scores for each clinical sign (redness, thickness, scaliness) of the face (score 0) at Week 8 were reclassified as tertiary in the Statistical Analysis Plan Update.

Quality of Life:

Change in QoL from baseline (Visit 1) to Week 8 using SF-36 (v2) and Skindex-16.

Safety:

Any reported adverse events (AEs), any reported adverse drug reactions (ADRs) and any local AEs reported on the face and the intertriginous areas. Reasons for withdrawal from the study.

Statistical methodology:

For the primary response criterion, subjects with 'controlled disease' according to the IGA of the face at Week 8, two hypotheses were tested at a 5% level of significance: 1) the efficacy of LEO 80190 ointment is not inferior to tacalcitol ointment and 2) the efficacy of

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LEO 80190 ointment is superior to the ointment vehicle. Both hypotheses were tested based on the full analysis set and the per protocol analysis sets. For the non-inferiority hypothesis 1, a two-sided 95% confidence interval (CI) for the difference in proportions was estimated using a Cochran-Mantel-Haenszel (CMH) test adjusted for country and non-inferiority was claimed if the lower limit of the CI was above −5%. For the superiority hypothesis 2, a CMH test adjusted for country was used. For the secondary response criteria, LEO 80190 ointment was compared to tacalcitol ointment and the ointment vehicle using CMH tests adjusted for country. Paired and two-sample t-tests were used to compare QoL data within and between treatment groups. Safety analysis was based on the safety analysis set for AEs, ADRs and lesional/perilesional AEs on the face and on the safety intertriginous analysis set for lesional/perilesional AEs on the intertriginous areas. The proportion of subjects who experienced AEs and ADRs were compared between the treatment groups using chi-square tests.

Summary – Conclusions

Treatment phase: enrolled; 782, randomised; 741, completers; 614. Observation phase: entered; 378, completers; 261. A total of 127 (17.1%) withdrew from the treatment phase; 22 (3.0%) due to unacceptable efficacy and 47 (6.3%) due to unacceptable adverse events.

At baseline, mean age was 48.5 years, 59.1% were male, 94.6% were White and 94.7% were Not Hispanic/Not Latino. Mean duration of psoriasis vulgaris was 16.7 years and mean extent was 7.9% of body surface area. Most subjects had moderate (52.9%) or mild disease (31.4%) according to the IGA of the face. The mean extent on the face was 31.9 cm² and mean TSS of the face was 5.9.

Efficacy results:

The proportion of subjects who achieved ‘controlled disease’ (IGA of the face) at Week 8 (LOCF) in the LEO 80190 ointment group was 56.8% compared with 46.4% in the tacalcitol ointment group and 36.3% in the ointment vehicle group. LEO80190 ointment was statistically significantly more effective than the ointment vehicle for the full analysis set (OR 2.40; 95% CI 1.51 to 3.82; p<0.001). The analysis of the per protocol analysis set supported these results. Based on the per protocol analysis set, LEO 80190 ointment was non inferior to tacalcitol ointment (difference 9.68; 95% CL 1.62 to 17.73) since the lower CI (1.62) was greater than −5%. Furthermore, the analysis for superiority, which was based on the full analysis set, showed that LEO 80190 ointment was statistically significantly more effective than tacalcitol ointment (difference 10.29; 95% CI 2.59 to 17.99; p=0.01). There was no treatment by country interactions in any of these analyses. The results for the secondary response criteria were as follows:

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	LEO 80190 Ointment (n=322)	Tacalcitol Ointment (n=317)	Ointment Vehicle (n=102)
Controlled disease (IGA of the face) n (%)			
Week 4 (LOCF)	151 (46.9)	94 (29.7)*	17 (16.7)*#
Success (TSS of the face) n (%)			
Week 8	164 (50.9)	123 (38.8)*	33 (32.4)*

	LEO 80190 Ointment (n=126)	Tacalcitol Ointment (n=129)	Ointment Vehicle (n=42)
Controlled disease (IGA of the intertriginous areas) n (%)			
Week 8	71 (56.3)	54 (41.9)*#	6 (14.3)*
Success (TSS of the intertriginous areas) n (%)			
Week 8	81 (64.3)	56 (43.4)*	9 (21.4)*

* comparison statistically significant in favour of LEO 80190 ointment when adjusted for multiplicity using the Hochberg approach
\# treatment by country interaction between LEO 80190 ointment and comparator

Among the subjects who were evaluated in the observation phase none of the subjects experienced rebound and the occurrence of relapse of the psoriasis was as follows:

Relapse of psoriasis on the face	LEO 80190 Ointment (n=171)	Tacalcitol Ointment (n=134)	Ointment Vehicle (n=32)
Relapse n(%)	76 (44.4)	47 (35.1)	8 (25.0)
Median time to relapse	64 days		

Relapse of psoriasis on the intertriginous areas	LEO 80190 Ointment (n=63)	Tacalcitol Ointment (n=51)	Ointment Vehicle (n=6)
Relapse n(%)	24 (38.1)	14 (27.5)	1 (16.7)

Quality of Life results:

In the SF-36 (v2) general health questionnaire there were no statistically significant changes from baseline to Week 8 in any treatment group for the Physical Component Summary. For the Mental Component Summary the change from baseline to Week 8 was statistically significant in both the LEO 80190 ointment and tacalcitol ointment groups ($p<0.001$ and $p=0.023$ respectively) but not in the ointment vehicle group. For the skin disease specific questionnaire (Skindex-16) the changes in the total score from baseline to Week 8 were statistically significant for all three treatments ($p<0.001$ for all groups).

Safety results:

In the treatment phase of the study, the proportion of subjects with at least one AE was similar between the LEO 80190 ointment group and the tacalcitol ointment group ($p= 0.20$) and the ointment vehicle group ($p=0.22$). The proportion of subjects with at least one ADR was lower in the LEO 80190 ointment and ointment vehicle groups than in the tacalcitol

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ointment group. The proportion of subjects with at least one lesional/perilesional AE on the face in the LEO 80190 ointment group was similar to the ointment vehicle (p=0.63) and statistically significantly lower than in the tacalcitol ointment group (p=0.006).

	LEO 80190 Ointment (n=321)	Tacalcitol Ointment (n=316)	Ointment Vehicle (n=102)
AEs n(%)	132 (41.4)	146 (46.2)	49 (48.0)
ADRs n(%)	48 (15.0)	84 (26.6)	17 (16.7)
Lesional/ perilesional AEs of the face n(%)	47 (14.6)	73 (23.1)*	13 (12.7)
Most common lesional/perilesional AEs of the face n(%)			
Erythema	12 (3.7)	28 (8.9)	2 (2.0)
Pruritus	8 (2.5)	11 (3.5)	4 (3.9)
Burning sensation	6 (1.9)	13 (4.1)	1 (1.0)
Skin irritation	4 (1.2)	10 (3.2)	1 (1.0)

* comparison statistically significant in favour of LEO 80190 ointment

The proportion of subjects with at least one lesional/perilesional AE on the intertriginous areas was similar between the LEO 80190 ointment group versus the tacalcitol ointment group (p= 0.33) and ointment vehicle group (p=0.15).

	LEO 80190 Ointment (n=138)	Tacalcitol Ointment (n=144)	Ointment Vehicle (n=45)
Lesional/ perilesional AEs of the intertriginous areas n(%)	9 (6.5)	14 (9.7)	6 (13.3)
Most common lesional/perilesional AEs of the intertriginous areas n(%)			
Erythema	1 (0.7)	4 (2.8)	0 (0.0)
Pruritus	2 (1.4)	3 (2.1)	1 (2.2)
Skin irritation	1 (0.7)	0 (0.0)	3 (6.7)
Psoriasis	1 (0.7)	2 (1.4)	2 (4.4)

Withdrawals due to AEs in the treatment phase were lower in the LEO 80190 ointment and ointment vehicle groups compared with the tacalcitol group; 16 (5.0%) subjects in the LEO 80190 ointment group and 6 (5.9%) subjects in the ointment vehicle group versus 29 (9.2%) subjects in the tacalcitol ointment group. In the LEO 80190 ointment group, the most common AE leading to withdrawal was psoriasis (4 subjects, 1.2%). In the tacalcitol ointment group the most common AEs leading to withdrawal were erythema (8 subjects, 2.5%) and psoriasis and burning sensation which accounted for withdrawal in 6 (1.9%) subjects each. In the ointment vehicle group the most common AE leading to withdrawal was pruritus in 2 (2.0%) subjects. There were no treatment related deaths. There was one

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serious adverse event (incision and drainage of a right olecranon abscess) in the ointment vehicle group that was considered possibly related to study medication. There were no treatment related serious adverse events in the LEO 80190 ointment and tacalcitol ointment groups.

Conclusion:

LEO 80190 ointment was statistically significantly more effective than tacalcitol ointment and the ointment vehicle for the treatment of psoriasis vulgaris on the face and on the intertriginous areas. The median time to relapse following successful treatment with LEO 80190 ointment was 64 days on the face and could not be calculated for the intertriginous areas. No rebound was observed. The improvement in skin related Quality of Life with LEO 80190 ointment was superior to both tacalcitol ointment and the ointment vehicle. The safety profile of LEO 80190 ointment was consistent with that observed in a previous study and the incidence of adverse drug reactions and lesional/perilesional AEs on the face and intertriginous areas was significantly lower than with tacalcitol ointment resulting in a more favourable benefit/risk ratio for LEO 80190 ointment.

Date of report:

23 October 2009

2.1 SCHEDULE/CHART OF STUDY PROCEDURES

		Treatment						Observation				
Visit	WP[a)]	1	2	3	4	5	6	FU[d)]	Extra visit[e)]	7	8	9
Day		0	7±2	14±2	28±2	42±2	56±2	+14±2		70±2	84±2	112±2
Week		0	1	2	4	6	8			10	12	16
Informed consent	X[b)]	X										
Inclusion criteria		X										
Exclusion criteria		X										
Medical history		X										
Physical examination		X										
Pregnancy test		X[c)]										
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X
Concurrent diagnoses		X										
Randomisation		X										
Investigator's assessment of extent of psoriasis vulgaris		X										
Investigator's global assessment of disease severity of the face		X	X	X	X	X	X		X	X	X	X
Investigator's assessment of clinical signs of the face		X	X	X	X	X	X					
Subject's global assessment of disease severity of the face		X	X	X	X	X	X					
Investigator's global assessment of disease severity of the intertriginous areas		X	X	X	X	X	X		X	X	X	X
Investigator's assessment of clinical signs of the intertrigi-nous areas		X	X	X	X	X	X					
Subject's global assessment of disease severity of the intertriginous areas		X	X	X	X	X	X					
Adverse event(s)		X	X	X	X	X	X	X	X	X	X	X
Compliance			X	X	X	X	X					
Quality of life		X					X					
Photos of psoriasis vulgaris on the face and on the intertriginous areas[f)]		X	X	X	X	X	X					
Supply of investigational product		X	X	X	X	X						
Collection of investigational product			X	X	X	X	X					

a) Prior to randomisation (Visit 1), a washout period (WP) (up to approximately 4 weeks) was completed if the subject was treated, or had recently been treated, with antipsoriatic treatments or other relevant medication, as defined in the exclusion criteria.

b) If the subject entered a washout period, an informed consent form was completed.

c) If female of childbearing potential.

d) Follow-up (FU) visit/contact: only applicable if an adverse event (serious or non-serious) classified as possibly or probably related to the investigational product or not assessable in relation to the investigational product was present at the subject's last on-treatment visit. This follow-up was performed 14 ± 2 days after the subject's last on-treatment visit or until final outcome of the adverse event was determined, whichever came first.

e) During the observation period, an extra visit was scheduled if a subject felt that reinitiation of treatment was necessary between 2 scheduled visits (after Visits 6, 7 or 8).
f) Photos were only taken at designated centres.

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ELECTRONIC SIGNATURES

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
[redacted]	[redacted], International Clinical Development Approval	10-dec-2009 11:24 GMT+01
[redacted]	[redacted] Biostatistics Approval	10-dec-2009 12:08 GMT+01