This document has been downloaded from www.leo-pharma.com subject to the terms of use state on the website. It contains data and results regarding approved and non-approved uses, formulations or treatment regimens, and it is provided for transparency and informational purposes only. The content does not reflect the complete results from all studies related to a product. As a document of scientific nature it is not to be seen as a recommendation or advice regarding the use of any products and you must always consult the specific prescribing information approved for the product prior to any prescription or use.

Clinical Study Report Synopsis

Calcipotriol Plus Hydrocortisone in 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 (LEO 80190 ointment) with calcipotriol 25 mcg/g in the ointment vehicle, hydrocortisone 10 mg/g in the ointment vehicle and the ointment vehicle alone, all applied once daily in the treatment of psoriasis vulgaris on the face and on the intertriginous areas, followed by a 52-week safety study in patients with psoriasis vulgaris on the face and on the intertriginous areas.

An international, multi-centre, prospective, randomised, double-blind, active- and vehicle-controlled, 4-arm, parallel group, 8-week clinical study followed by an open-label 52-week, single arm, safety study

Final Report of the 8-week double-blind, parallel group study and Interim Report (6-month data cut) of the open-label safety study

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

LEO 80190-O21
22-DEC-2010
EudraCT No. 2007-004782-18

1 CLINICAL STUDY REPORT SYNOPSIS APPROVAL

1.1 APPROVAL STATEMENT

On behalf of LEO, only the Head of 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] _____
Biostatistics, 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

Professor [redacted] _____
International Co-ordinating Investigator

2 SYNOPSIS

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

Title of study:

Calcipotriol Plus Hydrocortisone in Psoriasis Vulgaris on the Face and on the Intertriginous Areas / LEO 80190-O21

International Co-ordinating Investigator:

Professor [redacted] Germany

Trial sites:

Belgium 5, Croatia 5, Czech Republic 11, Germany 48, Hungary 12, Latvia 5, Macedonia 1, The Netherlands 4, Poland 17, Serbia 6, Slovenia 2

Publication (reference):

Not applicable

Studied period:	Phase of development:
First subject enrolled on 16-May-2008 Last subject completed on 11-JAN-2010	3

Objectives:

Primary objective

To compare the efficacy of once daily treatment for up to 8 weeks of an ointment containing calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g (LEO 80190 ointment) with calcipotriol 25 mcg/g in the ointment vehicle, hydrocortisone 10 mg/g in the ointment vehicle and the ointment vehicle alone in subjects with psoriasis vulgaris on the face.

Secondary Objectives

To compare the efficacy of once daily treatment for up to 8 weeks of LEO 80190 ointment, hydrocortisone 10 mg/g in the ointment vehicle and the ointment vehicle alone in subjects with psoriasis vulgaris on the intertriginous areas.

To compare the safety of once daily treatment for up to 8 weeks of LEO 80190 ointment with calcipotriol 25 mcg/g in the ointment vehicle, hydrocortisone 10 mg/g in the ointment vehicle and the ointment vehicle alone in subjects with psoriasis vulgaris on the face and on the intertriginous areas.

To evaluate the safety and efficacy of up to 60 weeks treatment of LEO 80190 ointment in psoriasis vulgaris on the face and on the intertriginous areas.

Methodology:

An international, multi-centre, prospective, randomised, double-blind, active- and vehicle-controlled, 4-arm, parallel group, 8-week, phase 3 clinical study in subjects with psoriasis

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

vulgaris on the face and on the intertriginous areas followed by an open-label, single-arm, 52-week safety study in a subgroup of subjects.

The subjects were stratified in two groups according to their level of psoriasis on the intertriginous areas at baseline. In the double-blind phase the subjects received topical treatment once daily for up to 8 weeks and were randomised 2:2:2:1 to LEO 80190 ointment, calcipotriol ointment, hydrocortisone ointment, or ointment vehicle.

In the open-label phase, subjects received LEO 80190 ointment applied once daily when required for up to an additional 52 weeks.

Number of subjects enrolled:

A total of 1245 subjects were enrolled and 1239 were randomised (353 to LEO 80190 ointment, 342 to calcipotriol ointment, 363 to hydrocortisone ointment and 181 to the ointment vehicle). Four hundred and ninety six subjects were enrolled in the long-term open-label phase, 454 of whom completed the double-blind phase and received treatment in the open-label phase.

Diagnosis and main criteria for eligibility:

Inclusion criteria

Hospital out-patients or subjects 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 cm² (the sum of all facial lesions) and a disease severity of at least mild according to the investigator's global assessment of disease severity (IGA) of the face. The treatment areas (the face and the intertriginous areas) had to be amenable to topical treatment with a maximum of 100 g of ointment per week 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, angiotensin-converting enzyme 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:

In the double-blind phase the investigational product was applied topically once daily, subjects received one of the following:

a) LEO 80190 ointment (calcipotriol 25 mcg/g plus hydrocortisone 10 mg/g ointment)
b) calcipotriol 25 mcg/g in the ointment vehicle
c) hydrocortisone 10 mg/g in the ointment vehicle
d) the ointment vehicle

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

In the open-label phase, LEO 80190 ointment was applied topically once daily, when required, for treatment of psoriasis vulgaris on the face and on the intertriginous areas.

Lot numbers: LEO 80190 ointment: 0731661, 0805262, 0821761, 0822161 and 0822162; calcipotriol ointment: 0734564, 0819162 and 0819161; hydrocortisone ointment: 0734563 and 0821762; ointment vehicle: 0731662 and 0819163.

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

Not applicable

Duration of treatment:

The treatment lasted for up to 8 weeks in the double-blind phase and for a subset of subjects this was extended with a further 52 weeks in the open-label phase.

Criteria for evaluation

Efficacy :

Efficacy was assessed by means of the IGA of the face and of the intertriginous areas (Visit 1 to end of trial), the Investigator's assessment of clinical signs (redness, thickness and scaliness) of the face and of the intertriginous areas (Visit 1 to Visit 6) and the patient's global assessment of disease severity of the face and of the intertriginous areas (Visit 1 to end of trial).

Primary response criterion:

Subjects with "controlled disease" according to the IGA of the face at Week 8.

For subjects with a baseline (Visit 1) severity of moderate or worse – "controlled disease" of the face was defined as clear or almost clear according to the IGA of the face. For subjects with a baseline severity of mild –"controlled disease" of the face was defined as clear according to the IGA of the face.

Secondary response criteria:

Subjects with "controlled disease" according to the IGA of the face at Week 4.

Subjects with "success" according to the Total Sign Score (TSS) of the face (scores 0 or 1) at Week 8.

Subjects with "controlled disease" according to IGA of the intertriginous areas at Week 8

Subjects with "success" according to TSS of the intertriginous areas at Week 8.

Safety:

Adverse events (AEs) (for the cutaneous AEs, location was recorded as face/intertriginous areas/other areas).

Safety evaluation:

AEs, adverse drug reactions (ADRs), lesional/perilesional AEs on the face and intertriginous areas.

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

AEs of concern associated with long term use of topical corticosteroids on the face and on the intertriginous areas during the long-term open-label phase.

Reasons for withdrawal from the study.

Statistical methodology

For the primary response criterion, the proportion of subjects with "controlled disease" at Week 8 according to the IGA of the face was compared between treatment groups using a Cochran-Mantel-Haenzel test adjusting for country. The odds-ratio (OR) (odds of success for LEO 80190 ointment relative to that of the other treatment group), its 95% confidence interval (CI) and P-value was calculated for all three comparisons. Each test was at a 5% level of significance. The Breslow-Day test for homogeneity of the OR across countries was performed. For the secondary efficacy criteria LEO 80190 ointment was compared to calcipotriol ointment, hydrocortisone ointment and the vehicle ointment using Cochran-Mantel-Haenszel tests adjusting for country.

The proportion of subjects who experienced AEs and ADRs, respectively, during the first 8 weeks of the study was compared between the treatment groups using the chi-square test. The proportion of subjects who experienced AEs on the face and on intertriginous areas, respectively, during the first 8 weeks of the study was also compared between the treatment groups using the chi-square test.

Summary – Conclusions

Efficacy results:

The primary analysis was to test for superiority of LEO 80190 ointment versus calcipotriol ointment, hydrocortisone ointment and the ointment vehicle using the full analysis set. LEO80190 ointment was not statistically significantly more effective than calcipotriol ointment (OR 1.28; 95% CI: 0.94 to 1.74; p=0.11) but was statistically significantly more effective than hydrocortisone ointment (OR 1.79; 95% CI: 1.31 to 2.45; p<0.001) and the ointment vehicle (OR 2.70; 95% CI: 1.80 to 4.04; p<0.001). Since all three tests needed to be significant for the study to be conclusive, the primary response criterion was not met.

	LEO 80190 ointment	Calcipotriol ointment	Hydrocortisone ointment	Ointment vehicle
number in full analysis set	353	341	363	180
Controlled disease IGA (face) at W8	44.8%	39.6%	31.7%	22.8%
Controlled disease IGA (face) at W4	28.6%	19.4%	16.8%	7.8%
Success TSS (face) at W8	48.4%	39.9%	36.1%	23.3%
Controlled disease IGA (intertriginous areas) at W8	46.8%	31.8%	26.4%	15.7%
Controlled disease IGA (intertriginous areas) at W4	26.3%	16.2%	13.7%	4.5%
Success TSS (intertriginous areas) at W8	48.0%	46.8%	32.4%	16.9%

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

At the start of the open-label phase, approximately 28% of subjects had 'controlled disease' of the face and of the intertriginous areas. The proportion of subjects with 'controlled disease' increased to approximately 40% for both the face and the intertriginous areas 4 weeks later at Week 12, and was between 48% and 70% (face) and 48% and 64% (intertriginous areas) at each subsequent visit to Week 60.

Safety results:

Double-blind Phase

The proportion of subjects with at least one AE was similar and not statistically significant between the treatment groups. The proportion of subjects with at least one ADR was statistically significantly lower for LEO 80190 ointment compared with calcipotriol ointment, (p=0.02) but not significantly different from hydrocortisone ointment or ointment vehicle. The number of subjects experiencing lesional/perilesional AEs of the face was not statistically significantly different between the treatment groups. However, the incidence of lesional/perilesional AEs on the intertriginous areas was statistically significantly lower in the LEO 80190 ointment group than in the calcipotriol ointment and ointment vehicle groups.

% subjects with at least one	LEO 80190 ointment	Calcipotriol ointment	Hydrocortisone ointment	Ointment vehicle
number in safety analysis set	351	341	362	181
AE	29.1%	32.0%	24.9	26.5%
ADR	9.7%	15.5%	6.9%	11.6%
Lesional/perilesional AE on the face	9.1%	11.7%	5.8%	9.4%
SAE	1.4%	1.5%	1.1%	0.0%
Withdrawal due to AE	3.1%	4.7%	2.2%	1.7%
number in intertriginous safety analysis set	181	187	194	94
Lesional/perilesional AE on the intertriginous areas	3.9%	10.7%	5.2%	11.7%

The most common lesional/perilesional AEs in the LEO 80190 ointment group were psoriasis (2.8% face and 1.7% intertriginous areas) followed by erythema (2.0% face); all other lesional/perilesional AEs were reported by less than 2% of subjects in the LEO 80190 ointment group. The incidence of lesional/perilesional psoriasis in the calcipotriol ointment group was 2.6% (face) and 3.7% (intertriginous areas), in the hydrocortisone group was 3.3% (face) and 3.1% (intertriginous areas) and for the ointment vehicle group was 3.9% (face) and 3.2% (intertriginous areas). The incidence of lesional/perilesional erythema on the face was 5.9% in the calcipotriol ointment group, 1.4% in the hydrocortisone ointment group, and 2.8% in the ointment vehicle group. Lesional/perilesional pruritus on the face was more frequent in the calcipotriol ointment group (3.8%) than in the other treatment groups (<2.0%). Most lesional/perilesional AEs were mild or moderate and the distribution of mild and moderate events was similar for the LEO 80190 ointment, hydrocortisone

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

ointment and ointment vehicle groups. In the calcipotriol ointment group there was a higher proportion of moderate lesional/perilesional AEs than for the other groups.

Fourteen subjects had SAEs during the double-blind phase. None of the SAEs were considered treatment-related. The incidence of withdrawals due to AEs in the double-blind phase was similar across the four treatment groups.

Long-term open-label LEO 80190 ointment treatment

A total of 266 subjects (58.7%) had at least one AE during the open-label phase. Most commonly, AEs affected the skin and subcutaneous tissue disorders SOC (31.1%) followed by infections and infestations SOC (28.9%). A total of 73 ADRs were reported for 61 subjects (13.5%). The most common ADRs were psoriasis (8.6%) and erythema (2.0%). All other ADRs were reported at incidences below 1.0% of subjects. The proportion of subjects experiencing lesional/perilesional AEs during the long-term open-label phase was 14.3% (face) and 15.2% (intertriginous areas). The most common lesional/perilesional AE was psoriasis (9.7% face and 11.7% intertriginous areas), followed by erythema (2.2% face). All other lesional/perilesional AEs were reported by less than 1% of subjects. The majority of lesional/perilesional AEs were mild or moderate.

Twenty-four subjects experienced 30 SAEs during long term treatment with open-label LEO 80190 ointment. Of these two cases of psoriasis were considered treatment related. During the open-label phase, 12 (2.6%) subjects withdrew due to 13 AEs. There was only one report of each event leading to withdrawal apart from psoriasis (2), erythema (2) and pregnancy (2). There were thee AEs in one subject considered associated with long-term corticosteroid use, pustular and fungal infection with onset during double-blind treatment (hydrocortisone ointment) and fungal infection with onset in the open-label period (LEO 80190 ointment). These three events were all mild in intensity. There were no other safety signals during open-label LEO 80190 ointment treatment.

Conclusion:

Although the proportion of subjects who achieved ‘controlled disease’ (IGA of the face) was higher in the LEO 80190 ointment group than the other treatment groups, the superiority of LEO 80190 ointment versus calcipotriol ointment, hydrocortisone ointment and the ointment vehicle was not confirmed for the treatment of psoriasis vulgaris on the face. The superiority of LEO 80190 ointment versus calcipotriol ointment, hydrocortisone ointment and the ointment vehicle was, however, indicated for the intertriginous areas. The safety profile of LEO 80190 ointment is similar to that observed in other studies and the product was well tolerated during long-term treatment.

Date of report:

22-DEC-2010

2.1 SCHEDULE/CHART OF STUDY PROCEDURES

Phase	**Double-blind Phase**							**Open Phase***	
Visit	**WP[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7 – 19[g]**	**FU[d]**
Day		**0**	**7±2**	**14±2**	**28±2**	**42±2**	**56±2**	**Week 12-60 ±7 days**	**+14±2**
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
Concurrent diagnoses		X							
Randomisation		X							
Investigator's assessment of extent of psoriasis vulgaris		X							
Investigator's global assessment (IGA) of disease severity of the face		X	X	X	X	X	X	X	
Investigator's assessment of clinical signs of the face		X	X	X	X	X	X		
Patient's global assessment of disease severity of the face		X	X	X	X	X	X	X	
IGA of disease severity of the intertriginous areas		X	X	X	X	X	X	X	
Investigator's assessment of clinical signs of the intertriginous areas		X	X	X	X	X	X		
Patient's global assessment of disease severity of the intertriginous areas		X	X	X	X	X	X	X	
Adverse event(s)		X	X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X	
Photos of psoriasis vulgaris on the face and on the intertriginous areas [e)]		X	X	X	X	X	X		
Supply of investigational product		X	X	X	X	X	X[f]	X[h]	
Collection of investigational product			X	X	X	X	X	X	

* Only the designated 450 subjects

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 WP, an informed consent form had to be completed.

c) If female of childbearing potential.

d) Follow-up (FU) visit/contact: only applicable if an AE (serious or non-serious) classified as possibly or probably related to the study medication or not assessable in relation to the study medication was present at

the subject's last on-treatment visit. This FU had to be performed 14 ± 2 days after the subject's last on-treatment visit or until final outcome of the AE was determined, whichever came first.

e) Photographs were only taken at designated centres.

f) At Visit 6 the supply of the open-label phase investigational product took place but only to the designated 450 subjects

g) Visits were performed every 4 weeks

h) At the last visit (Visit 19) investigational product was not supplied

LEO 80190-O21 Clinical Study Report Synopsis EudraCT No. 2007-004782-18 22-Dec-2010 - English

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] Biostatistics Approval	04-jan-2011 12:09 GMT+01
[redacted]	[redacted], International Clinical Development Approval	08-jan-2011 16:52 GMT+01