Clinical Study Protocol

Effect of Calcipotriol plus Betamethasone Dipropionate Gel on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to 16 Years, 11 months) with Scalp and Body Psoriasis

A phase 2 trial evaluating the safety and efficacy of once daily use of LEO 80185 gel containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis

An international, multi-centre, prospective, non-controlled, open, single-group, 8-week trial in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis

ICH GCP statement: *The clinical trial will be conducted in compliance with the Clinical Study Protocol, GCP and the applicable regulatory requirement(s).*

LEO Pharma A/S	**Protocol Code Number:**	**LP0076-1017**
Global Clinical Operations	**Date:**	**17-Apr-2013**
	Version:	**1**
	EudraCT Number:	**2013-001538-16**

1 Clinical Study Protocol Approval/Acknowledge

1.1 Approval Statement LEO Pharma A/S

On behalf of LEO Pharma A/S, only the head of Medical Department and the head of Biostatistics and Data Management are authorised to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following persons have approved this Clinical Study Protocol using electronic signatures as presented on the last page of this document:

PPD

Head of Biostatistics and Data Management

PPD

Head of Medical Department

1.2 Approval Statement International Co-ordinating Investigator

It is the responsibility of the international co-ordinating investigator to approve the Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s).

The following person has approved this Clinical Study Protocol by manually signing the International Co-ordinating Investigator Clinical Study Protocol Approval Form adjoined as a separate page to this document:

Lawrence F. Eichenfield, MD

International co-ordinating investigator

1.3 Acknowledge Statement Investigator(s)

Each participating investigator must agree to the approved Clinical Study Protocol and Consolidated Clinical Study Protocol(s) comprising any subsequent amendment(s) by signing the Investigator (Consolidated) Clinical Study Protocol Agreement Form.

2 Protocol Statement

2.1 Compliance with Good Clinical Practice

This Clinical Study Protocol is designed to comply with the guideline produced by the International Conference on Harmonisation (ICH) on the topic Good Clinical Practice (GCP) as well as other relevant guidelines issued by ICH, primarily the efficacy guidelines.

2.2 Trademarks

Daivobet®, Dovobet®, Taclonex®, Xamiol®, Daivonex®, and Dovonex® are trademarks owned by LEO Pharma A/S (or its subsidiaries). Daivobet® gel is launched in different markets under following trademarks Daivobet®, Dovobet®, Taclonex®, and Xamiol®. The U.S. marketed product, Taclonex® topical suspension, is equivalent to Daivobet® gel marketed in other markets.

3 Protocol Synopsis

Name of finished/ investigational product:	LEO 80185 gel Taclonex® gel
Name of active substance:	Calcipotriol plus betamethasone dipropionate.
Title of trial/ protocol code number:	Effect of Calcipotriol plus Betamethasone Dipropionate Gel on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to 16 Years, 11 months) with Scalp and Body Psoriasis / LP0076-1017
Co-ordinating investigator(s):	Lawrence F. Eichenfield, MD, University of California at San Diego/Rady Children´s Hospital, California, USA
Estimated number of trial sites and distribution:	Approximately 30 sites: Australia and New Zealand: Approximately 5 sites Canada: Approximately 5 sites France: Approximately 3 sites Germany: Approximately 5 sites United Kingdom: Approximately 5 sites USA: Approximately 7 sites
Trial period:	Planned date of enrolment of first subject: October 2013. Planned date of completion of last subject: October 2015.
Main objectives:	The primary objective is to evaluate the safety of once daily use of calcipotriol (50 mcg/g) plus betamethasone

(0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

The secondary objective is to evaluate the efficacy of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

Methodology:

An international, multi-centre, prospective, non-controlled, open, single-group, 8-week trial in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis

Psoriatic lesions on the scalp and body will be treated with calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel applied once daily for up to 8 weeks under maximal use conditions on the body.

The duration of the trial for each subject will be a maximum of 20 weeks, consisting of a screening period of 7 days to 8 weeks followed by a 4- or 8-week treatment period and, if required, a 2-4-week follow-up period.

Prior to Visit 1 (Day 0), a wash-out period (up to 8 weeks) should be completed if the subject is being treated or has recently been treated with anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria.

During the trial, the subset of subjects performing HPA axis assessments will be allowed to use non-steroid topical treatments without expected systemic effects to treat psoriasis lesions on the face and sensitive areas (armpits, groin, under the breasts and in other skin folds around the genitals and buttocks). Subjects not performing HPA axis assessments will be allowed to use any topical treatment

allowed except potent or very potent (WHO groups III-IV) corticosteroids to treat psoriasis lesions on the face and skin folds. Bath oils and moisturizing soaps are allowed. Topical vitamin D analogues (calcipotriol, calcitriol or tacalcitol) are limited to a maximum of 50 g, 75 g or 100 g of ointment/gel/cream per week depending on the subject's age and body surface area (BSA). This includes the amount of investigational product used.

The study will consist of a wash-out period (if required), 2 screening visits; SV1 and SV2 (to be conducted within 8 and 1 weeks prior to Visit 1, respectively) followed by a 4-or 8-week treatment period (Days 0-56). Subjects whose psoriasis is clear after 4-week treatment will stop the investigational product and leave the trial. Subjects who have signs of psoriasis after 4 weeks of treatment will continue treatment for another 4-week period. During the treatment period, the study visits will be on Days 0, 14, 28, 42 and 56 (Visits 1 to 5).

Each subject will receive the investigational product and will be instructed to apply it once daily.

Calcium metabolism evaluation will be performed at SV2 and after 4 and 8 weeks of treatment (Day 28 and Day 56). The evaluation will include measurements of serum calcium, albumin, phosphate, plasma parathyroid hormone (PTH) level and calculation of the albumin-corrected serum calcium concentration. Also, 24-hour urine will be collected and urinary volume, calcium-, phosphate-, and creatinine excretion will be measured and the calcium:creatinine and phosphate:creatinine ratios calculated.

Pharmacokinetic analysis will be performed to evaluate if any potential adverse events could be correlated to the investigational product. A blood sample for

pharmacokinetic analysis will be drawn at Visit 3 (Day 28) for the measurement of plasma LEO 80185 when the investigational product is at a steady state concentration.

In the U.S. only, subjects will perform hypothalamic-pituitary-adrenal (HPA) axis function assessments until 30 evaluable subjects are obtained. These subjects will have their HPA axis function assessed at SV2 and after 4 and 8 weeks of treatment (Day 28 and Day 56). The adrenal function will be assessed with a rapid standard dose synthetic adrenocorticotropic hormone (ACTH) (CORTROSYN®) challenge test. The test consists of blood sampling starting at 8 a.m. (± 30 minutes). Following the blood sample, an intravenous bolus injection of 250 mcg CORTROSYN® is given at time zero (t=0). Serum cortisol concentration at 30 and 60 minutes will reflect the stimulation induced by CORTROSYN®. Subjects will not be included in the study if serum cortisol concentration at SV2 is 5 mcg/dl or lower before the CORTROSYN® injection or if serum cortisol concentration, obtained at 30 minutes after CORTROSYN® injection, is below or equal to 18 mcg/dl. At Week 4, subjects with serum cortisol below or equal to 18 mcg/dl at 30 min after administration of CORTROSYN® will discontinue the treatment and will perform a follow-up visit 2 (Visit FU2).

Visit FU2 will be conducted for subjects with possible HPA axis suppression 28 days after possible suppression is reported (i.e. 28 days after Visit 3 or 5). This follow-up will involve a repeat HPA axis suppression test to assess if the possible suppression has reversed.

A follow-up visit (Visit FU1) will be conducted 14 days after the last on-treatment visit for subjects with any ongoing adverse event(s) classified as possibly/probably related/not assessable relationship to the investigational

product. FU1 will also be performed for subjects with albumin corrected serum calcium *above* the reference range at the last on-treatment visit.

A window of ± 2 days will be allowed for Visits 2, 3, 4, 5, FU1 and FU2. The overall treatment period should be 4 or 8 weeks (28 or 56 days ± 2 days).

Number of subjects to be enrolled:

In total, a sufficient number of subjects will be enrolled to ensure 100 subjects are evaluable for calcium metabolism. Thirty of the 100 subjects will also be evaluable for HPA axis suppression. At least 30 subjects will be evaluable for pharmacokinetic evaluation.

In the U.S. only, subjects will perform hypothalamic-pituitary-adrenal (HPA) axis function assessments until 30 evaluable subjects are obtained.

Power of the study

No formal sample size calculation evaluating the power of the study has been performed, but further considerations regarding sample size have been made as described below.

The upper limit of an exact two-sided 95% confidence interval for the probability of observing a specific adverse event, when 0 out of 100 possible events have been observed, is approximately 4% assuming a binomial distribution.

With 100 subjects and an assumed response rate (percentage of subjects who achieve “Clear” or “Almost clear” according to the Investigator’s Global Assessment (IGA) of disease severity on the body at end of treatment) of approximately 30%, the 95% confidence interval for the estimated response rate will be approximately ± 9%.

Main criteria for inclusion for *all* subjects:

1. Signed informed consent given by parent(s), or legal guardian(s), or by the subject (according to national

law) following their receipt of verbal and written information about the trial.

2. Subjects will receive verbal and written information and will provide written assent to the trial.
3. Subjects 12 to 16 years, 11 months of age.
4. Either sex.
5. Any race or ethnicity.
6. Clinical signs of psoriasis vulgaris on both the scalp and body (trunk and/or limbs).
7. At SV2 and Visit 1, a clinical diagnosis of scalp and body (trunk and/or limbs) psoriasis which is:
    a. of an extent of 10 to 35% of the body surface area (excluding psoriatic lesions of the face and sensitive areas. Sensitive areas include armpits, groin, under the breasts and in other skin folds around the genitals and buttocks), and
    b. of at least moderate severity according to the investigator's global assessment of disease severity on the body, and
    c. for subjects aged 12 to 14 years with a BSA ≤ 1.3 m^2, amenable to topical treatment with a maximum of 50 g of investigational product per week, and
    d. for subjects aged 12 to 14 years with a BSA > 1.3 m^2, amenable to topical treatment with a maximum of 75 g of investigational product per week, and
    e. for subjects aged 15 to 16 years, 11 months with a BSA ≤ 1.7 m^2, amenable to topical treatment with a maximum of 75 g of investigational product per week, and
    f. for subjects aged 15 to 16 years, 11 months with a BSA > 1.7 m^2, amenable to topical treatment with a maximum of 100 g of investigational product per week.
8. A serum albumin-corrected calcium below the upper

reference limit at SV2.

9. Females of child-bearing potential must have a negative urine pregnancy test result and must agree to use a highly effective method of contraception during the trial. Highly effective methods are defined as ones which result in a low failure rate (less than 1% per year) such as progestin-only formulations (implants, injectables, or "mini-pill" in combination with a barrier method), some intra-uterine devices, double barrier methods (e.g. cervical cap and condom), tubal ligation/section, sexual abstinence or vasectomised partner. The patients must have used the contraceptive method for at least 1 month prior to the pregnancy test, and must continue using the contraceptive method for at least 1 week after the last application of investigational product. A female is defined as not of child-bearing potential if she is premenarchal, postmenopausal or surgically sterile (hysterectomy or bilateral ovariectomy).
10. Subjects fulfilling national requirements/law for participation in this trial.

Additional inclusion criteria for subjects performing HPA axis assessments (U.S. only):

1. At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:
    a. more than or equal to 20% of the scalp area, and
    b. of at least moderate severity according to the investigator's global assessment of disease severity on the scalp.
2. Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dl before ACTH challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge.

Additional inclusion criteria for subjects *not* performing HPA axis assessments:

1. At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:
    a. more than or equal to 10% of the scalp area, and

b. of at least moderate severity according to the investigator's global assessment of disease severity on the scalp.

Main exclusion criteria for *all* subjects:

1. A history of hypersensitivity to any component of the LEO 80185 gel
2. Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on scalp and/or body psoriasis within the following time period prior to Visit 1 and during the trial:
    a. etanercept – within 4 weeks prior to Visit 1
    b. adalimumab, infliximab – within 2 months prior to Visit 1
    c. ustekinumab – within 4 months prior to Visit 1
    d. experimental products – within 4 weeks/5 half-lives (whichever is longer) prior to Visit 1
3. Systemic treatment with therapies other than biologicals, with a possible effect on scalp and/or body psoriasis (e.g., retinoids, immunosuppressants, PUVA) within 4 weeks prior to Visit 1 (Day 0) or during the trial.
4. UVB therapy within 2 weeks prior to Visit 1 or during the trial.
5. Any topical treatment on the scalp and body (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1 or during the trial.
6. Systemic calcium, vitamin D supplements, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the trial.
7. Planned initiation of, or changes to, concomitant medication that could affect psoriasis (e.g., betablockers, chloroquine, lithium, ACE inhibitors) during the trial.
8. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
9. Subjects with any of the following conditions present on the treatment areas on scalp and/or body: viral (e.g., herpes or varicella) lesions of the skin, 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.

10. Other inflammatory skin diseases that may confound the evaluation of scalp and/or body psoriasis.
11. Planned excessive exposure to sun during the trial that may affect scalp and/or body psoriasis.
12. Known or suspected severe renal insufficiency or severe hepatic disorders.
13. Known or suspected disorders of calcium metabolism associated with hypercalcaemia.
14. 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.
15. Current participation in any other interventional clinical trial.
16. Previously enrolled in this trial.
17. Subjects who have received treatment with any non-marketed drug substance (i.e., an agent which has not yet been made available for clinical use following registration) within a month prior to SV1 or longer, if the class of substance required a longer wash-out as defined above (e.g., biological treatments).
18. Subjects or parent(s) or legal guardian(s) known or suspected of being unlikely to comply with the Clinical Trial Protocol (e.g., alcoholism, drug dependency or psychotic state).
19. Females who are pregnant, or of child-bearing potential and wishing to become pregnant during the trial, or who are breast-feeding.
20. Females of child-bearing potential with positive pregnancy test at SV2.
21. Subject (or their partner) not using an adequate method of contraception according to national

requirements.

Additional exclusion criteria for subjects performing HPA axis assessments (U.S. only):

1. A history of serious allergy, allergic asthma or serious allergic skin rash.
2. Known or suspected hypersensitivity to any component of CORTROSYN® (including ACTH/cosyntropin/tetracosactide).
3. Systemic treatment with corticosteroids (including inhaled and nasal steroids) within 12 weeks prior to SV2 or during the trial.
4. Topical treatment with corticosteroids within 2 weeks prior to SV2 or during the trial.
5. Oestrogen therapy (including contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity within 4 weeks prior to SV2 or during the trial.
6. Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the trial.
7. Systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole) within 4 weeks prior to SV2 or during the trial. Topical ketoconazole 2 weeks prior to SV2.
8. Hypoglycemic sulfonamides within 4 weeks prior to SV2 or during the trial.
9. Antidepressive medications within 4 weeks prior to SV2 or during the trial.
10. Known or suspected endocrine disorder that may affect the results of the ACTH challenge test.
11. Clinical signs or symptoms of Cushing's disease or Addison's disease.
12. Subjects with diabetes mellitus.
13. Known or suspected cardiac condition.
14. Not following nocturnal sleep patterns.

Additional exclusion criteria for subjects *not* performing HPA axis assessments:

1. Topical treatment on the trunk and/or limbs with very potent (WHO group IV) corticosteroids within 2 weeks prior to Visit 1 or during the trial.
2. Topical treatment on the face and/or sensitive areas

	(armpits, groin, under the breasts and in other skin folds around the genitals and buttocks) with potent or very potent (WHO groups III-IV) corticosteroids within 2 weeks prior to Visit 1 or during the trial.
Investigational product:	Calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) gel (LEO 80185 gel). CORTROSYN® will be used only as a test product for the ACTH challenge testing.
Reference product:	Not applicable
Duration of treatment:	The screening period including any washout period will last for 7-56 days, depending on the prior use of excluded treatments. The treatment period will be up to 8 weeks. The follow-up period will last for up to 4 weeks, depending on whether the subject has potential adrenal suppression and/or ongoing adverse event(s) classified as possibly/probably related/not assessable relationship to the investigational product.
Assessments:	**Safety Assessment** Calcium metabolism evaluation will include serum albumin-corrected calcium, phosphate and plasma PTH on a blood sample taken at SV2 and after 4 and 8 weeks of treatment. 24-hour urine will be collected at SV2 and after 4 and 8 weeks of treatment and urinary volume, calcium-, phosphate-, and creatinine excretion will be measured and calcium:creatinine and phosphate:creatinine ratios will be calculated. Dietary calcium intake will be monitored 3 days prior to and during collection of 24-hour urine. Subjects will be instructed to keep a diary of daily intake of calcium-rich nutrients in these periods. Blood pressure will be measured at SV2, Visit 3 (Day 28) and Visit 5 (Day 56). Laboratory screening: the following laboratory tests will

be taken at SV2, Visit 3 (Day 28) and Visit 5 (Day 56):

- haematology: hemoglobin, haematocrit, red blood cells (RBC), mean corpuscular volume (MCV), white blood cells (WBC) including differential count and platelets.
- biochemistry (serum/plasma): cortisol, urea, creatinine, albumin, sodium, potassium, chloride, calcium, phosphate and PTH.
- urinalysis on 24-hour urine: calcium, phosphate, creatinine, volume.
- urinalysis on spot urine: glucose and ketones.

A PK sample will be collected at Visit 3 prior to the application of investigational product on the day of the visit.

Urinary pregnancy test will be performed at SV2, Visit 3 (Day 28), Visit 5 (Day 56) and at FU2 (if applicable) in females of childbearing potential.

Adverse events will be recorded at all visits after SV1 (if applicable).

For subjects performing HPA axis assessments: the ACTH challenge test will be performed on 3 occasions: At SV2, Visit 3 (Day 28) and Visit 5 (Day 56). In addition, an ACTH challenge test will be performed at Visit FU2 for subjects with possible HPA axis suppression at Visit 3 or Visit 5.

Efficacy Assessment

At SV2 and at all on-treatment visits the following will be performed:

- Investigator's Global Assessment (IGA) of disease severity on the body (ranging from "Clear" to "Severe")
- Investigator's Global Assessment of disease severity

	on the scalp (ranging from “Clear” to “Severe”) • Investigator’s assessment of the extent and severity of clinical signs of psoriasis vulgaris (redness, thickness and scaliness) • Patient’s global assessment of disease severity on the body (ranging from “Clear” to “Severe”) • Patient’s global assessment of disease severity on the scalp (ranging from “Clear” to “Severe”) • Patient’s assessment of itching on the scalp and body • Patient’s assessment of sleep
Safety Evaluation:	• Adverse drug reactions (ADRs)
Primary response criteria:	• Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 and at Week 8 • Change in albumin-corrected serum calcium from baseline (SV2) to Week 4, Week 8, and end of treatment • Change in 24-hour urinary calcium excretion from baseline (SV2) to Week 4, Week 8, and end of treatment
Secondary response criteria:	• Adverse events (AEs) • Subjects with serum cortisol concentration of ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4 and at Week 8 • Change in urinary calcium:creatinine ratio from baseline (SV2) to Week 4 and Week 8
Efficacy Evaluation: **Secondary response criteria:**	• Subjects with “Controlled disease” (i.e., “Clear” or “Almost clear”) according to the investigator’s global assessment of disease severity on the body at end of treatment. • Percentage change in PASI from baseline to end of treatment. • Subjects with “Controlled disease” (i.e., “Clear” or “Very mild”) according to the patient’s global assessment of disease severity on the body at end of treatment.

Statistical methods:

The percentages of subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes, and at both 30 and 60 minutes, after the ACTH-challenge at Week 4 and Week 8 will be calculated. The mean serum cortisol concentration at time 0 and at 30 and 60 minutes after ACTH-challenge at baseline (SV2), Week 4 and Week 8, respectively, will be calculated.

The number of subjects experiencing each type of adverse event and each type of adverse drug reaction will be tabulated.

The mean change from baseline (SV2) to Week 4 and Week 8 in haematology, biochemistry and urinalysis parameters except in the urinary glucose and ketones will be calculated. For the albumin-corrected serum calcium and 24-hour urinary calcium excretion, the mean change from baseline to end of treatment will also be calculated and the 95% confidence interval of mean change from baseline to Week 4 and Week 8 and end of treatment will be presented. For the urinary calcium:creatinine ratio, the 95% confidence interval of mean change from baseline to Week 4 and Week 8 will be presented. Laboratory parameters will also be categorised according to the reference range, and shift tables will be produced.

The following will be presented with the 95% confidence interval:

- the percentage of subjects with “Controlled disease” according to the investigator’s global assessment of disease severity on the body at end of treatment
- the percentage change in PASI from baseline to end of treatment
- the percentage of subjects with “Controlled disease” according to the patient’s global assessment of disease severity on the body at end of treatment

3.1 Schedule/Chart of Trial Procedures

Visit	**SV1** [1]	**SV2** [1,2]	**1**	**2**	**3**	**4**	**5**[3]	**FU1**[4]	**FU2**[5]
Day	**-56 to -7**	**-7 to -3**	**0**	**14 ± 2**	**28 ± 2**	**42 ± 2**	**56 ± 2**	**+ 14 ± 2**	**+ 28 ± 2**
Informed consent	X								
Demographics	X								
Medical history	X								
Physical examination	X								
Height, weight and BSA	X	X							
Inclusion/exclusion criteria	X	X	X						
Vital signs (blood pressure, heart rate)		X			X		X		
Haematology/biochemistry/ urinalysis [6]		X			X		X	X [7]	
Pharmacokinetic blood sample [8]					X				
ACTH challenge test [9]		X			X		X		X
Instruction for 24-hour urine collection and dietary calcium intake diary	X			X		X			
Review of dietary calcium		X			X		X		
Collection of 24-hour urine [10]		X			X		X		
Urine pregnancy test [11, 12]		X			X		X		
Adverse events		X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
Investigator's assessment of extent of psoriasis (BSA) and extent of scalp psoriasis		X	X						
Investigator 's global assessment of disease severity on the scalp and on the body		X	X	X	X	X	X		
Patient's global assessment of disease severity on the scalp and on the body		X	X	X	X	X	X		
Investigator's assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)		X	X	X	X	X	X		
Patient's assessment of itching and sleep		X	X	X	X	X	X		
Dispensing of IP			X	X	X	X			
Return of IP				X	X	X	X		
IP Compliance				X	X	X	X		

1. There should be at least 4 days between SV1 and SV2 so dietary information (diary) can be collected.

2. It will be acceptable that the following assessments are done on the day prior to the ACTH challenge: vital signs, spot urine collection, pregnancy test, AEs, concomitant medication and assessments of psoriasis.
3. In case of early withdrawal prior to Visit 5, the additional tests scheduled for Visit 5 should be done at the end of treatment, with the exception of the ACTH-challenge test and the 24-hour urine collection.
4. Follow-up Visit 1 is only applicable for subjects who at the last on-treatment visit have ongoing (serious or non-serious) adverse event(s) classified as possibly/probably related/not assessable relationship to the investigational product and for subjects with albumin corrected serum calcium *above* reference range at the last on-treatment visit.
5. Applicable only to subjects in the U.S. performing HPA axis assessments. Follow-up Visit 2 is only applicable if serum cortisol is ≤18 mcg/dl at 30 min after the ACTH challenge test at Visit 3 or Visit 5.
6. Blood and spot urine samples should be collected at the end of treatment for subjects who are withdrawn from trial prior to Visit 5.
7. If laboratory results suggest albumin corrected serum calcium *above* reference range at the last on-treatment visit, a follow-up test will be performed.
8. PK sample to be taken prior to the application of investigational product on the day of the visit.
9. Applicable only to subjects in the U.S. performing HPA axis assessments. ACTH challenge test should be performed at 8.00 a.m. ±30 min after checking vital signs and collecting blood and urine samples.
10. It will be acceptable that the 24-hour urine sample is collected up to three days prior to the trial visit.
11. For female subjects of childbearing potential.
12. In case of early withdrawal there will be a pregnancy test if possible at their last on treatment visit.

Table of Contents

4 List of Abbreviations and Definition of Terms

4.1 List of Abbreviations

ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
ADR	Adverse drug reaction
AE	Adverse event
BSA	Body surface area
CI	Confidence interval
CRF	Case report form (the CRF could be electronic)
CRO	Contract research organisation
eCRF	Electronic CRF
EMEA	European Medicines Agency
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good Clinical Practice
HPA	Hypothalamic-pituitary-adrenal
ICH	International Conference on Harmonisation
ICTM	International clinical trial manager
IEC	Independent ethics committee
IGA	Investigator's global assessment
IP	Investigational product
IRB	Institutional Review Board
LEO	LEO Pharma A/S
MCV	Mean corpuscular volume
Mcg	Microgram
MedDRA®	Medical Dictionary for Regulatory Activities
NLCRA	National lead clinical research associate
PK	Pharmacokinetics
PUVA	Psoralen-ultraviolet A
PTH	Parathyroid hormone
RBC	Red blood cells
SAE	Serious adverse event
SD	Standard deviation
SDV	Source data verification
SOP	Standard operating procedure
SV	Screening visit

UVA	Ultraviolet A light
UVB	Ultraviolet B light
U.S.	United States
WBC	White blood cells
WHO	World Health Organisation

4.2 Definition of Terms

Assessment

A (cluster of) characteristic(s) measured and/or recorded for a subject.

Certified Copy

A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original (FDA Guidance for Industry, Computerized Systems Used in Clinical Investigations, May 2007).

Concomitant Medication

Any medication taken by a subject during the clinical trial apart from the investigational product.

Enrolled Subject

A subject for whom informed consent has been obtained and a CRF number assigned.

Fraud

Fabrication of data, selective and undisclosed rejection of undesired results, substitution with fictitious data, deliberately incorrect use of statistical methods for the purposes of reaching other conclusions than those warranted by the data, misinterpretation of results and conclusions, plagiarism of results or entire articles from other researchers, misrepresentation of other researchers' results, unwarranted authorship, and misleading application for positions or funds.

International Clinical Trial Manager (ICTM)

The person appointed by LEO Pharma A/S to be the main international representative responsible for all aspects of a clinical trial as outlined in Global Clinical Operations SOPs.

Clinical trial agreement

A contract between on the one hand LEO Pharma A/S and/or a Contract Research Organisation (CRO) and on the other hand an investigator and/or the institution specifying the conditions for the co-operation in the clinical trial and the investigator's and/or the institution's responsibilities.

Investigator Staff Signature Form

A form used:

1. for the investigator to delegate trial related tasks/duties
2. for trial site staff to sign and date to accept delegation
3. for trial site staff to document signature and initials
4. for the investigator to authorise tasks/duties delegated

Investigator Trial File

The collection of trial documents required by Global Clinical Operations SOPs LEO Pharma A/S, ICH Guidelines and/or regulatory requirements to be on file at the trial site.

LEO Pharma A/S

LEO Pharma A/S refers to the sponsor of the clinical trial.

LEO Pharma A/S affiliate

An affiliated company of LEO Pharma A/S authorised to manage certain clinical trial related activities for LEO Pharma A/S.

Monitor

A person appointed by LEO Pharma A/S to carry out monitoring of a clinical trial.

National Lead CRA (NLCRA)

The person appointed by LEO Pharma A/S to be the national representative responsible for all aspects of a clinical trial within a country as outlined in Global Clinical Operations SOPs.

Response Criterion

An assessment or a transformation of the assessment(s) described on a subject level for which a statistical analysis is performed, i.e. a p-value or a confidence interval is stated, or for which tabulation serves as important supportive evidence of efficacy/safety.

Subject Identification List

A summary list kept by the investigator in the Investigator Trial File which records the names of all subjects enrolled and the date of enrolment in the trial at that trial site. The list includes each subject's corresponding CRF number to allow the investigator/institution to reveal the identity of any subject if required.

Subject Screening Log

A document kept by the investigator which identifies patients/subjects who entered pre-trial screening.

Subject Screening Log is synonymous with Patient Screening Log.

Subject Study Card

A card given to a subject by the trial site at the time investigational product is first dispensed to a subject to identify that the subject is having treatment with an investigational product.

Writing committee

An appointed committee participating in the writing of a multi-centre publication.

5 Ethics

5.1 Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs)

The clinical trial must be approved by/receive favourable opinion from relevant Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) prior to the enrolment of subjects.

Any amendments to the approved clinical trial must likewise, as required, be approved by/receive favourable opinion from relevant IRBs/IECs prior to implementation.

The appropriate regulatory authority(ies) must be notified of/approve the clinical trial, as required.

5.2 Ethical Conduct of the Trial

This clinical trial will be conducted to conform to the principles of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and last revised in Seoul in October 2008 by the WMA General Assembly (see Appendix II).

5.3 Ethical Consideration Statement

Psoriasis vulgaris is a chronic and recurrent skin disorder. At present, no curative treatment is available for the disease. Psoriasis is a disabling disease, with a significant impact on the quality of life comparable with that observed in other chronic medical conditions such as diabetes and depression (1) (2).

Approximately 35% of patients with psoriasis develop the disease before the age of 20 and 25% are diagnosed between 10 and 19 years of age (3). Involvement of the scalp is more common in children (4) (5). Based on this, it is evident that scalp psoriasis is also prevalent in the adolescent age group (12-17 years).

Most preparations are greasy and messy to apply, have an unpleasant smell and may cause staining of clothes and fabrics and skin irritation (6). Patient's compliance is therefore often poor, leading to a bad therapeutic result. Therefore, there is a need for a patient acceptable topical treatment in this age group.

LEO 80185 gel is a fixed combination product containing the vitamin D_3 analogue calcipotriol and betamethasone dipropionate, for topical treatment of psoriasis vulgaris on scalp and body in subjects aged 18 years and above.

Daivobet® gel was approved for the treatment of scalp psoriasis in adults in several countries in the EU and the US in 2008 and is launched under the trademarks Daivobet®, Dovobet®, Taclonex®, and Xamiol®. Since then it has been approved in the remaining EU countries (2009) and in several other countries in the rest of the world (more than 40 countries outside EU), including Canada and Australia; approvals are pending in several countries in the rest of the world. The product has been launched with the indication scalp psoriasis in adults since 2008.

The marketing authorisation application for treatment of 'non-scalp' psoriasis vulgaris in adults was approved in several countries in the EU in July 2009. Since then, the indication of non-scalp psoriasis vulgaris in adults has been approved in the remaining EU countries (Dec 2011), in US October 2012, and in several other countries in the rest of the world. Approvals are pending in several countries in the rest of the world. The product was launched in the first European country, Denmark, in March 2010 under the trademark Daivobet® gel.

Two non-controlled trials, MBL 0801 and MBL0412 INT, in adolescent subjects (aged 12-17 years) with psoriasis on the scalp have recently been completed. In a total of 109 adolescent subjects using up to 69 g/week, LEO gel was safe and effective in the treatment of psoriasis vulgaris on the scalp. The effects on calcium metabolism were investigated; no cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was assessed in a subset of 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment which was considered mild (7) (8).

All subjects in the trial will receive LEO 80185 gel to use once-daily for up to 8 weeks. This application frequency and treatment duration have been shown to be safe and effective in adults for the approved products Taclonex® and Xamiol®.

At the end of the trial, subjects will have received treatment with LEO 80185 gel for up to 8 weeks. Continued use of LEO 80185 gel at the end of the trial will not be available to the subjects.

Following the 4-week or 8-week treatment period and the follow-up examinations, subjects will leave the trial and, if required, resume the treatment they received prior to the wash-out period or start a treatment according to the investigator's discretion, whichever is most appropriate.

The parent(s)/legal guardian(s) of the subjects will give informed consent, and subjects must give their assent, or subjects may give informed consent as appropriate and according to national laws and regulations.

Laboratory evidence of adrenal insufficiency due to the use of topical corticosteroid treatment has been reported (9), due to systemic absorption of the corticosteroid. LEO 80185 gel contains the corticosteroid betamethasone dipropionate and is why adrenal function will be assessed in the present trial, although the risk of adrenal suppression with LEO 80185 gel is expected to be low.

In this trial, treatment for up to 8 weeks is expected to be safe. The application area of LEO 80185 gel for subjects in the trial is expected to decrease with time as their psoriasis decreases in severity. Thus, the amount of investigational product required is expected to be less by the end of the trial. Adrenal function will be assessed by an ACTH-challenge test before, during, and at the end of trial treatment. This test involves injecting a synthetic subunit of ACTH (CORTROSYN®) into the subject, and measuring the cortisol produced by the adrenal glands 30 and 60 minutes after the injection.

The use of CORTROSYN® in this trial will be in keeping with that detailed in the US Prescribing Information (Appendix III); therefore this is expected to be of low risk.

The risk of hypercalcemia due to systemic absorption of the calcipotriol component of LEO 80185 gel is expected to be low when the medication is used in the doses specified in the trial. Any potential effects of LEO 80185 gel on calcium metabolism will be assessed by measurement of the concentrations of serum calcium and -phosphate and plasma parathyroid hormone (PTH) and the urinary calcium-, phosphate-, and creatinine excretion based on collection of 24-hour urine and the calcium:creatinine and phosphate:creatinine, ratios will be calculated before, during and at the end of treatment.

The expected total blood volume collected will be approximately 46.5 ml for subjects performing HPA axis assessments and 31.5 ml for subjects not performing HPA axis assessments. This excludes any follow-up assessment of abnormal values. Topical anaesthetic will be provided at study sites to decrease discomfort and pain for the subjects when having placed catheters at the (sub)investigator's discretion.

Recruitment for the trial will be continued until 100 subjects are available for evaluation of calcium metabolism. This includes the 30 subjects (in the US) without adrenal suppression at baseline who is to undergo ACTH-challenge test at end of treatment (Visit 3 or 5).

Since all subjects will receive the LEO 80185 gel, the prospect of subjects experiencing an improvement of their psoriasis during the trial will be good. Subjects will be under the careful supervision of a dermatologist with paediatric experience during the entire course of the trial. Subjects performing HPA axis assessments will be allowed to use non-steroid topical treatments without expected systemic effects to treat psoriasis lesions on the face and skin folds. Subjects not performing HPA axis assessments will be allowed to use any topical treatment allowed except potent or very potent (WHO groups III-IV) corticosteroids to treat psoriasis lesions on the face and skin folds. Bath oils and moisturizing soaps are allowed.

The results from this trial could help make LEO 80185 gel available to adolescent subjects suffering from psoriasis. It is therefore concluded that the expected benefits of conducting this trial will compensate for the inconveniences for the participating subjects.

5.4 Subject Information and Informed Consent

The parent(s)/legal guardian(s) of subjects will receive written and verbal information concerning the trial or subjects may give informed consent as appropriate and according to national laws or regulations. This information will emphasise that participation in the trial is voluntary and that the subject may withdraw from the trial at any time and for any reason. The parent(s)/legal guardian(s) will be given an opportunity to ask questions and will be given sufficient time to consider before consenting. Signed and dated informed consent for the subject to participate in the trial will be obtained from the parent(s)/legal guardian(s), or by the subject in accordance with national laws or regulations, prior to any trial related procedure being carried out.

All subjects will also receive appropriate written and verbal information, be given an opportunity to ask questions and sufficient time to consider, before providing written assent. The subject's decision not to participate or to withdraw will be respected, even if consent is given by the parent(s)/legal guardian(s).

If during the trial a subject who has previously given assent becomes legally emancipated i.e. ceases to be a minor, the subject should be asked to provide their written consent.

All Investigators will sign an "Investigator's Agreement" to confirm the above.

5.5 Handling of Personal Data

Subjects (or their legally acceptable representative) shall be asked to consent that their personal data are recorded, collected, processed and may be transferred to EU and non-EU countries in accordance with any national legislation regulating privacy and data protection.

Personal data shall be handled and processed by all relevant parties involved in the clinical trial in accordance with any national legislation regulating privacy and data protection as well as in accordance with the general terms and conditions of the authorisation granted by the Danish Data Protection Agency to LEO Pharma A/S as set forth in the attached Appendix I. LEO Pharma A/S is considered data controller for this clinical trial.

6 Trial Administrative Structure

6.1 Sponsor

LEO Pharma A/S is the sponsor of the clinical trial.

6.2 LEO Pharma A/S Affiliates and CRO(s)

LEO Pharma A/S has transferred certain clinical trial related activities to the LEO Pharma A/S affiliate(s) and/or to the CRO(s) relevant for the conduct of the clinical trial.

LEO Pharma A/S affiliates

LEO Pharma Inc. 1 Sylvan Way, Parsippany, NJ 07054, USA.
LEO Pharma Inc. 123 Commerce Valley Drive East, Suite 400, Thornhill, Ontario, L3T 7W8, Canada.
LEO Pharma. 2 Rue Rene Caudron, 78960 Voisins-le-Bretonneux, France.
LEO Pharma. Longwick Road, Princes Risborough, HP27 9RR, Buckinghamshire, United Kingdom.
LEO Pharma GmbH. Frankfurter Strasse 233, A3, 63263 Neu-Isenburg, Germany.
LEO Pharma Pty Ltd, Level 3, Tower One, 25 Montpelier Rd, Bowen Hills QLD 4006, Australia.

Clinical Research Organizations

PPD ,PPD ,PPD ,PPD, PPD A.

The CRO will be responsible for all services related to the central laboratory analysis (haematology, biochemistry, urinalysis) as agreed to in a Service Agreement/Contract.

PPD ,PPD ,PPD ,PPD ,PPD.

The CRO will be responsible for all services related to the laboratory PK analysis as agreed to in a Service Agreement/Contract.

6.3 LEO Pharma A/S Personnel

6.3.1 International Clinical Trial Manager (ICTM)

PPD , Clinical Project Manager, LEO Pharma Inc., 123 Commerce Valley Drive East, Suite 400, Thornhill, Ontario, L3T 7W8, Canada. Tel.: +1-PPD , Fax: +1-PPD , e-mail: PPD @leo-pharma.com

6.3.2 National Lead CRA (NLCRA)

PPD , Senior Clinical Research Associate, 1 Sylvan Way, Parsippany, NJ 07054, USA, Tel: +1 PPD , Fax: +1 PPD , email: PPD @leo-pharma.com

Other NLCRA contact details to be provided outside protocol.

6.3.3 Sponsor's Medical Expert

PPD , MD, Medical Expert, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark. Tel: +45 PPD , email: PPD @leo-pharma.com

6.3.4 Safety Scientist, Global Pharmacovigilance

PPD , Pharmacovigilance Scientist, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark, Tel: +45 PPD , email: PPD @leo-pharma.com

6.3.5 Study Statistician

PPD , MSc, Principal Statistician, LEO Pharma A/S, Industriparken 55, DK-2750 Ballerup, Denmark. Tel.: +45 PPD , e-mail: PPD @leo-pharma.com

6.3.6 Study Data Manager

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6.4 Protocol Authors

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6.5 Investigators and Trial Committees

6.5.1 International Co-ordinating Investigator

The international co-ordinating investigator is responsible for approval of the (Consolidated) Clinical Study Protocol, Clinical Study Protocol Addendum(s), (Consolidated) CRF and the Clinical Study Report on behalf of all trial investigators and as agreed to in an International Co-ordinating Investigator Agreement.

Lawrence F. Eichenfield, MD, University of California at San Diego/Rady Children's Hospital, Pediatric and Adolescent Dermatology, 8010 Frost Street-Suite 602, San Diego, California CA 92123, USA, Tel.: +1 858 576 1700, Fax: +1 858 966 4040, e-mail: leichenfield@rchsd.org

6.5.2 National Co-ordinating Investigator(s)

The National Co-ordinating Investigators are responsible for national issues relating to the clinical trial as agreed to in a National Co-ordinating Investigator Agreement.

The contact details of National Co-ordinating Investigators are provided outside the protocol.

6.5.3 Investigators

Each participating investigator is responsible for all aspects of the clinical trial conduct at his/her trial site as agreed to in a clinical trial agreement.

The contact details of each participating investigator are provided outside the protocol and in the national clinical trial applications.

6.5.4 Trial Committees

Not Applicable

6.6 Agreements

Before the initiation of any clinical trial related activities by the investigators/clinical trial committee(s)/LEO Pharma A/S affiliate(s)/CRO(s) listed above, the relevant parties must have entered into a written agreement regulating those activities.

7 Insurance

LEO Pharma A/S has taken out relevant insurances covering the subjects in the present clinical trial in accordance with applicable laws and regulations.

8 Introduction and Rationale

8.1 Psoriasis

Psoriasis is one of the most common chronic skin diseases, with a prevalence generally estimated at between 1 to 3% of the world's population (10). Psoriasis is characterised by sharply marginated areas of affected skin which appear thickened, red and scaly, and may itch. This appearance is produced by a greatly increased rate of epidermal proliferation with impaired differentiation of keratinocytes. Dermal blood vessels are dilated and there is infiltration of the skin with immunologically active cells (11) (12). The pathogenesis is incompletely understood, but the disease is thought to be triggered by activation of the cellular immune system with involvement of T cells, dendritic cells, and various cytokines and chemochines (13).

The most common clinical type of psoriasis, affecting 80-90% of patients, is psoriasis vulgaris (plaque-type psoriasis) (14). Sites of predilection are the hairy scalp (30% initially and 75% over the course of the disease), the extensor surfaces of the elbows and knees and the sacral region (15). The nails are involved in about 30% of patients with psoriasis and in about 20% psoriatic arthritis arises, usually many years after the initial cutaneous manifestation.

Psoriasis can be treated either by topical therapy, phototherapy, or by systemic methods (10) (16). Systemic treatments and phototherapy are generally reserved for extensive disease unresponsive to topical treatments due to concerns over toxicity (13) (16).

Most preparations are greasy and messy to apply, have an unpleasant smell and may cause staining of clothes and fabrics and skin irritation (6). Patient's compliance is therefore often poor, leading to a bad therapeutic result.

There is a need for a patient acceptable topical treatment.

8.2 Investigational Product Description

LEO 80185 (Calcipotriol plus Betamethasone Dipropionate) Gel

LEO 80185 gel, containing calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate), is a topical therapy indicated for treatment of psoriasis vulgaris on the scalp and body. It obtained marketing approval in 2008 in the U.S., Canada, and 16 European countries, and since then has been marketed in the U.S. and Europe under the trade names Taclonex® Scalp Topical Suspension and Daivobet®/Dovobet®/Xamiol® gel, respectively. In this Clinical Study Report, 'LEO 80185 gel' is used in text 'LEO 80185' is used in the tables, figures, and listings.

Calcipotriol is a vitamin D_3 analogue and betamethasone dipropionate is a topical corticosteroid. Both the active components in LEO 80185 gel have been widely available world-wide for many years and their efficacy and safety profiles in the treatment of psoriasis are well-known.

Numerous trials have been conducted with LEO 80185 gel as described in the Investigator's Brochure. Overall, it can be concluded that LEO 80185 gel is considered to be effective and safe in the treatment of psoriasis vulgaris on scalp and body.

8.3 Trial Rationale

The FDA has approved Taclonex® Gel for the treatment of body psoriasis in adults. The objective of the present phase 2 trial is to evaluate the safety and efficacy of LEO 80185 gel for the treatment of both body and scalp psoriasis in adolescent subjects and has been undertaken as a post-marketing commitment to the FDA (for NDA 22-185). The FDA requires the trial to be conducted in 100 evaluable paediatric patients (ages 12 to 16 years, 11 months) with psoriasis vulgaris on the scalp and body, to evaluate the safety and effect of Taclonex® Gel on calcium metabolism. In a subset of a least 30 patients treated under maximal use conditions, evaluation of the hypothalamic-pituitary axis and pharmacokinetics is required.

LEO 80185 gel has marketing approval in many countries for the treatment of scalp psoriasis in adults. Two non-controlled trials, MBL 0801 and MBL 0412 INT, in adolescent subjects (aged 12-17 years) have recently been completed. In these trials in a total of 109 adolescent subjects, LEO gel was safe and effective in the treatment of psoriasis vulgaris on the scalp (7) (8).

Approximately 35% of patients with psoriasis develop the disease before the age of 20 and 25% are diagnosed between 10 and 19 years of age (3). Involvement of the scalp is more common in children (4) (5). Based on this, it is evident that scalp psoriasis is also prevalent in the adolescent age group (12-17 years).

Only 10% of psoriasis patients develop psoriasis before the age of ten (3). The clinical appearance of psoriasis in children (ages 2-11 years) may differ from the classical picture seen in older patients. Facial psoriasis is more common in children than in adults and may be the only site affected; guttate and flexural forms are particularly common in children (20) (21) (22) (23). Children have a higher body surface area (BSA) to body mass ratio than adolescents and adults which increases the potential for adverse drug reactions due to absorption of topically applied compounds through the skin (24). This limits the use of potent topical corticosteroids in this age group (25). Hence children below 12 years of age will not be enrolled into this study.

To evaluate the safety of the LEO 80185 gel in this trial, all adverse events reported by the subject or observed by the investigator will be recorded. In addition, any effects resulting from systemic absorption of the active components, betamethasone dipropionate and calcipotriol, will be evaluated by assessing adrenal function and calcium metabolism, respectively.

Laboratory evidence of adrenal insufficiency due to the use of topical corticosteroid treatment has been reported (9). This is due to systemic absorption of the corticosteroid, which then induces suppression of the hypothalamic-pituitary-adrenal (HPA) axis due to a negative feedback effect on the pituitary gland and the hypothalamus (9) (26). This results in a decrease in the secretion of ACTH from the pituitary gland. The adrenal glands depend on ACTH as a tropic hormone in such a way that ACTH deficiency results in a reversible inability to produce cortisol (27). Hence, the adrenal glands lose the capacity to produce cortisol in response to an ACTH-challenge. Adrenal function can therefore be measured by injection of a synthetic subunit of ACTH into the subject, and then measuring the production of cortisol by the adrenal glands in response to this. A serum cortisol concentration of 18 mcg/dl or less at 30 and 60 minutes after the injection indicates possible adrenal suppression (26).

The effect of LEO 80185 gel on adrenal function in adult subjects has been assessed by the ACTH-challenge test in a previous trial (28). The subjects included in the trial had extensive psoriasis on both scalp (at least 30% of scalp affected) and non-scalp regions of the body (15-30% of body surface area). Subjects applied LEO 80185 gel to lesions on the scalp and the corresponding ointment product Daivobet®/Taclonex® ointment to the lesions on the trunk and limbs. After a total of 32 subjects had received treatment with LEO 80185 gel for 4 weeks, 5 had a serum cortisol concentration ≤18mcg/dl at 30 minutes after ACTH-challenge, and out of 11 subjects who continued treatment for 8 weeks, 2 subjects had a serum cortisol of ≤18 mcg/dl at 30 minutes after ACTH challenge. The cortisol value was >18mcg/dl at 60 minutes after ACTH-challenge for all subjects.

In the two trials MBL 0801 and MBL 0412 INT, no cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was measured in 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment which was considered to be mild (7) (8).

In the present study LEO 80185 gel will be applied to lesions on both scalp and body. The risk of adrenal suppression with LEO 80185 gel is expected to be low with LEO 80185 being applied under maximal use conditions as systemic exposure is known to be low and the drug concentration is expected to be below the limit of quantification (Investigator's Brochure).

Subjects participating in the present study will perform ACTH-challenge test before and after treatment. The pre-treatment test is to ensure that adrenal function is normal before starting investigational product. Serum cortisol concentrations at 30 and 60 minutes after injection will be measured in order to show the maximum cortisol level achieved (26).

Overdosage with topical calcipotriol can cause hypercalcemia (27), due to the systemic absorption of calcipotriol, which then affects calcium metabolism as it is a vitamin D analogue. However, extensive experience with topical use of calcipotriol in psoriasis has demonstrated no significant impact on calcium metabolism when used in the recommended amounts (maximum weekly dose in adults of 100 g of a 50 mcg/g concentration). Doses up to 300 g have been used with serum calcium remaining within the normal range (29).

Two studies with calcipotriol ointment have been conducted in children 2-14 years of age and did not show effects on calcium metabolism (30) (31). One trial with Daivobet® Ointment, MCB 0501 INT, has been conducted in adolescent subjects and did not show any effects on calcium or HPA axis.

Calcium metabolism will be evaluated in the present study by 24-hour urinary collection and measurement of serum calcium, -phosphate and plasma PTH before, during and/or after treatment. 24-hour urine will be collected and the urinary calcium-, phosphate- and creatinine excretion will be measured and the calcium:creatinine and phosphate:creatinine ratios calculated. Subjects who report an incomplete 24-hour urinary collection will be excluded from the analyses of 24-hour urinary calcium and phosphate excretion but will still be analysed for calcium:creatinine and phosphate:creatinine. To identify any severe, non-reported sampling errors the daily creatinine excretion/kg body weight will be calculated as proposed by Remer et al. (32).

It is well established that there is a relationship between dietary calcium intake and the urinary calcium excretion in adults. However, in rapidly growing adolescents, it appears that only dietary calcium intake above a certain threshold of approximately 1500 mg/day will result in an increase in urinary calcium excretion (33). As this study includes adolescents 12 to 16 years, 11 months of age, some of the subjects may not be in phase of rapid growth and some subjects might consume large amounts of dairy products. Therefore, there is a possibility of an effect of the diet on the calcium excretion.

A review of the subject's normal diet will be done. As dairy products account for approximately 73% of the total dietary calcium content, and as the calcium from other sources such as vegetables and grains are less easily absorbed (34), the review will focus on the intake of dairy products. The subjects will be asked to keep a diary of the daily intake of dairy products and calcium-fortified products (e.g. bread, cereals, orange juice or soy milk). The number of daily servings of calcium defined as one cup (240 ml) or 1.5 ounces of cheese (43 g) in dairy products such as milk, yoghurt or cheese or of a calcium-fortified product with corresponding calcium content (300 mg calcium/cup) will be estimated (35). The subjects will be asked to keep the same number of daily servings three days prior to and during each 24-hour urine collection. The number of daily calcium servings should not exceed five (i.e. 1500 mg calcium).

The combination of high calcium intake with vitamin D supplementation, or extreme calcium intake alone, has been shown to significantly increase urinary calcium in adults (36). Hence, the use of calcium or vitamin D supplements will be excluded in this study.

Subjects will apply the LEO 80185 gel once daily for up to 8 weeks. This application frequency and treatment duration has been shown to be safe and effective in adults with 55-70% of subjects achieving controlled disease after 4-week treatment (37) (38). Only subjects who have signs of scalp and/or body psoriasis after 4 weeks of treatment will continue treatment in the study. As the application area and the amount of investigational product required is expected to decrease with time as lesions heal, continued treatment for up to 8 weeks is expected to be safe in those subjects who need it.

The maximum weekly dosage approved for adults is 100 g. In the present trial, the maximum weekly dose will be determined by age and BSA at baseline. For subjects aged 12 to 14 years with a BSA $\leq$ 1.3 m^2, the maximum weekly dosage will be 50 g of LEO 80185 gel per week. For subjects aged 12 to 14 years with a BSA > 1.3 m^2 and subjects aged 15 to 16 years, 11 months with a BSA $\leq$ 1.7 m^2, the maximum weekly dosage will be 75 g of LEO 80185 gel per week. For subjects aged 15 to 16 years, 11 months with a BSA > 1.7 m^2, the maximum weekly dosage will be 100 g of LEO 80185 gel per week.

To be eligible for the study, all subjects are to have an extent of scalp and body (trunk and /or limbs) psoriasis of 10-35% BSA. In addition, subjects performing HPA axis assessments are to have an extent of scalp psoriasis that is more than or equal to 20% of the scalp area. Subjects not performing HPA axis assessments are to have an extent of scalp psoriasis that is more than or equal to 10% of the scalp area. The disease severity of body psoriasis and scalp psoriasis is to at least moderate according to the investigator's global assessment. It is expected that many adolescent subjects with psoriasis will have less extensive and less severe disease. However, since the main purpose of the present study is to evaluate the safety of the investigational product, the exposure to treatment has to be as close to maximum as possible.

A total of 100 subjects will be enrolled in this study. All subjects will undergo assessments on safety, pharmacokinetic analysis, calcium metabolism and efficacy. A subgroup of 30 subjects providing data for the ACTH-challenge test at the end of treatment will be included in the study. This number of subjects has been requested by the FDA for an HPA axis evaluation. Pharmacokinetic analysis will be performed to evaluate if any adverse events could be correlated to the investigational product. A blood sample (2 x 6mL) for pharmacokinetic evaluation will be drawn at Visit 3 (4 weeks of treatment) prior to the application of LEO 80185 on the day of the visit. Validated bioanalytical assays will be used for quantification of calcipotriol, betamethasone dipropionate and the metabolites MC1080 and betamethasone 17-propionate in the plasma sample.

Subjects will have a washout period of up to 8 weeks if they are using treatments which could have an effect on (or be affected by) the ACTH-challenge test (e.g., corticosteroids, enzymatic inductors, cytochrome P450 inhibitors, hypoglycemic sulfonamides, antidepressive medications, estrogen), calcium metabolism (e.g., vitamin D, calcium supplements, antacids, diuretics and antiepileptics) or the psoriasis to be treated with investigational product (e.g., systemic/topical/ ultraviolet anti-psoriatic therapy, although emollients are allowed).

9 Trial Objectives

9.1 Primary Objective

The primary objective is to evaluate the safety of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

9.2 Secondary Objectives

The secondary objective is to evaluate the efficacy of once daily use of calcipotriol (50 mcg/g) plus betamethasone (0.5 mg/g) (as dipropionate) gel in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

10 Investigational Plan

10.1 Trial Design

This will be an international, multi-centre, prospective, non-controlled, open, single-group, 8-week trial in adolescent subjects (aged 12 to 16 years, 11 months) with scalp and body psoriasis.

The subjects will receive topical treatment with calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g (as dipropionate) gel once daily for up to 8 weeks.

Washout/Screening Period

Depending on the prior use of disallowed treatments, the washout/screening period will last for 7 to 56 days prior to the first administration of LEO 80185 gel (Visit 1).

Prior to attending any study procedure, a signed informed consent must be obtained from the parent(s)/legal guardian(s) of the subject, or by the subject (as appropriate and according to national laws and regulations). Written assent should also be obtained from the subject. There are two screening visits: Screening visit 1 (SV1) and screening Visit 2 (SV2). Depending on the subjects' use of excluded treatments, SV1 is performed up to 7 weeks before SV2; SV2 is performed at 3 to 7 days before Visit 1.

Treatment Period

The treatment period will last for up to 8 weeks. There are up to 5 visits: Visit 1 (day 0), Visit 2 (day 14), Visit 3 (day 28), Visit 4 (day 42) and Visit 5 (day 56). Visits 2-5 should be performed within ±2 days of the scheduled time relative to Visit 1; if they are outside this window, the (sub)investigator should record the reason in the subject's medical record.

LEO 80185 gel will be applied once daily to scalp psoriasis lesions. Subjects should be instructed to discontinue treatment on individual lesions if/when a lesion has cleared. Subjects whose psoriasis clears after 4-week treatment will stop the investigational product and leave the trial.

Subjects who have psoriasis after 4 weeks of treatment will continue treatment for another 4-week period.

Subjects whose psoriasis clears at Visit 2 or Visit 4 according to the (sub)investigator should discontinue treatment but will stay in the study. During periods of discontinuation of treatment the subject should restart the treatment if psoriasis reappears.

Follow-up

If applicable, the treatment period will be followed by a follow-up (FU) period consisting of visit FU1 and/or visit FU2.

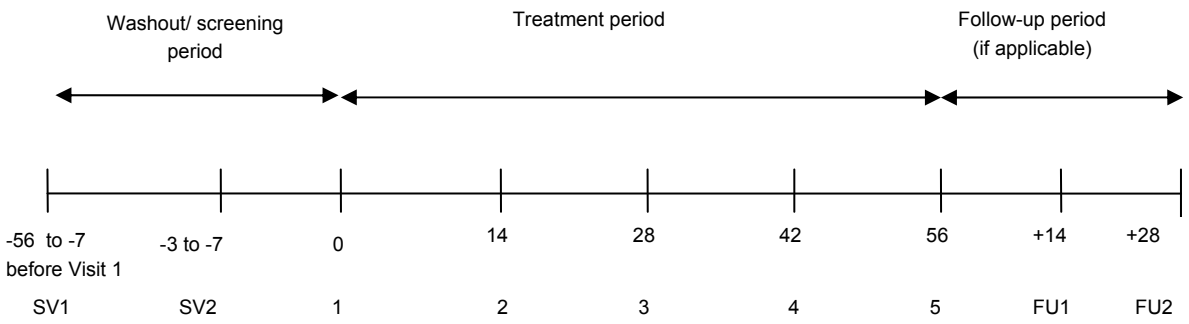
Visit FU1 will take place 14 days after the last visit in the treatment period, but only if there was an ongoing adverse event at this time of possible/probable/not assessable relationship to the investigational product. At the (sub)investigator's discretion, the information required at this visit may be obtained over the telephone, and the subject need not make the visit. FU1 should also be performed if albumin corrected serum calcium is *above* the reference range at the last on-site visit. A new blood sample should then be collected.

Visit FU2 will take place 28 days after the ACTH-challenge test performed at Visit 3 or Visit 5, but only if this test showed a serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH-challenge.

Visits FU1 and FU2 should be performed within ±2 days of the scheduled time; if they are outside this window, the qualified site staff person should record the reason in the subject's medical record/source document.

For details, see Section 10.8 for the schedule of trial procedures.

10.1.1 Overall Chart



There should be at least 4 days between SV1 and SV2 so dietary information (diary) can be collected.

10.2 Time Schedule

Planned date of enrolment of first subject: October 2013

Planned date of enrolment of last subject: August 2015

Planned date of completion of last subject: October 2015

10.3 Number of Subjects/Sample Size

Enrolment of subjects will continue until data from 100 subjects are available for evaluation of the effect of LEO 80185 on calcium metabolism (i.e. the measurement of the serum calcium concentration and the 24-hour urinary calcium excretion and/or the urinary calcium:creatinine ratio is available before and at Visit 3 and/or Visit 5). Therefore, the number of enrolled subjects can exceed 100 subjects.

The 100 subjects include the enrolment of 30 evaluable subjects in the U.S. without adrenal suppression at baseline who undergo the ACTH-challenge test at end of treatment (Visit 3 or Visit 5). At the time the sponsor confirms 30 evaluable subjects has been obtained, there may be other subjects ongoing in the trial that have not yet had the ACTH-challenge test. Such subjects will be allowed to complete the trial without the ACTH-challenge test.

The primary objective of the trial is to evaluate the safety of LEO 80185 gel. No formal sample size calculation evaluating the power of the trial has been performed. However, a few considerations regarding the sample size have been made as described below.

The upper limit of an exact two-sided 95% confidence interval for the probability of observing a specific adverse event, when 0 out of 100 possible events have been observed, is approximately 4% assuming a binomial distribution.

With 100 subjects and an assumed response rate (percentage of subjects who achieve “Clear” or “Almost clear” according to the investigator’s global assessment of disease severity on the body at end of treatment) of approximately 30%, the 95% confidence interval for the estimated response rate will be approximately ± 9%.

Each centre should aim to enroll a minimum of three subjects. As the subjects are anticipated to be difficult to recruit, the suggested minimum number of subjects per centre is based on practical considerations rather than statistical robustness of estimates given per centre.

10.4 Criteria for Subject Selection (In- and Exclusion)

Following receipt of verbal and written information about the trial, the parent(s) or legal guardian(s) or the subject (as appropriate and according to national laws or regulations) must provide **signed and dated informed consent** before any trial related activity is carried out, including activities relating to washout periods.

Any implementation of national requirements/law for the trial subject’s participation in the clinical trial will be ensured and will be described in submission documentation to authorities/ethics committees, as applicable.

10.4.1 Inclusion Criteria

10.4.1.1 Inclusion Criteria for *All* Subjects

1. Signed informed consent given by parent(s), or legal guardian(s), or by the subject (according to national law) following their receipt of verbal and written information about the trial.
2. Subjects will receive verbal and written information and will provide written assent to the trial.
3. Subjects 12 to 16 years, 11 months of age.
4. Either sex.
5. Any race or ethnicity.
6. Clinical signs of psoriasis vulgaris on both the scalp and body (trunk and/or limbs).
7. At SV2 and Visit 1, a clinical diagnosis of scalp and body (trunk and/or limbs) psoriasis which is:
    a. of an extent of 10 to 35% of the body surface area (excluding psoriatic lesions of the face and sensitive areas. Sensitive areas include armpits, groin, under the breasts and in other skin folds around the genitals and buttocks), and
    b. of at least moderate severity according to the investigator's global assessment of disease severity on the body, and
    c. for subjects aged 12 to 14 years with a BSA $\leq$ 1.3 m^2, amenable to topical treatment with a maximum of 50 g of investigational product per week, and
    d. for subjects aged 12 to 14 years with a BSA > 1.3 m^2, amenable to topical treatment with a maximum of 75 g of investigational product per week, and
    e. for subjects aged 15 to 16 years, 11 months with a BSA $\leq$ 1.7 m^2, amenable to topical treatment with a maximum of 75 g of investigational product per week, and
    f. for subjects aged 15 to 16 years, 11 months with a BSA > 1.7 m^2, amenable to topical treatment with a maximum of 100 g of investigational product per week.
8. A serum albumin-corrected calcium below the upper reference limit at SV2.

9. Females of child-bearing potential must have a negative urine pregnancy test result and must agree to use a highly effective method of contraception during the trial. Highly effective methods are defined as ones which result in a low failure rate (less than 1% per year) such as progestin-only formulations (implants, injectables, or "mini-pill" in combination with a barrier method), some intra-uterine devices, double barrier methods (eg. cervical cap and condom), tubal ligation/section, sexual abstinence or vasectomised partner. The patients must have used the contraceptive method for at least 1 month prior to the pregnancy test, and must continue using the contraceptive method for at least 1 week after the last application of investigational product. A female is defined as not of child-bearing potential if she is premenarchal, postmenopausal or surgically sterile (hysterectomy or bilateral ovariectomy).
10. Subjects fulfilling national requirements/law for participation in this trial.

10.4.1.2 Additional Inclusion Criteria for Subjects Performing HPA Axis Assessments (U.S. only)

1. At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:
    a. more than or equal to 20% of the scalp area, and
    b. of at least moderate severity according to the investigator's global assessment of disease severity on the scalp.
2. Subjects with a normal HPA axis function at SV2 including serum cortisol concentration above 5 mcg/dl before ACTH challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge.

10.4.1.3 Additional Inclusion Criteria for Subjects *Not* Performing HPA Axis Assessments

1. At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:
    a. more than or equal to 10% of the scalp area, and
    b. of at least moderate severity according to the investigator's global assessment of disease severity on the scalp.

10.4.2 Exclusion Criteria

10.4.2.1 Exclusion Criteria for *All* Subjects

1. A history of hypersensitivity to any component of the LEO 80185 gel
2. Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on scalp and/or body psoriasis within the following time period prior to Visit 1 and during the trial:
    a. etanercept – within 4 weeks prior to Visit 1

   b. adalimumab, infliximab – within 2 months prior to Visit 1
   c. ustekinumab – within 4 months prior to Visit 1
   d. experimental products – within 4 weeks/5 half-lives (whichever is longer) prior to Visit 1
3. Systemic treatment with therapies other than biologicals, with a possible effect on scalp and/or body psoriasis (e.g., retinoids, immunosuppressants, PUVA) within 4 weeks prior to Visit 1 (Day 0) or during the trial.
4. UVB therapy within 2 weeks prior to Visit 1 or during the trial.
5. Any topical treatment on the scalp and body (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1 or during the trial.
6. Systemic calcium, vitamin D supplements, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the trial.
7. Planned initiation of, or changes to, concomitant medication that could affect psoriasis (e.g., betablockers, chloroquine, lithium, ACE inhibitors) during the trial.
8. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
9. Subjects with any of the following conditions present on the treatment areas on scalp and/or body: viral (e.g., herpes or varicella) lesions of the skin, 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.
10. Other inflammatory skin diseases that may confound the evaluation of scalp and/or body psoriasis.
11. Planned excessive exposure to sun during the trial that may affect scalp and/or body psoriasis.
12. Known or suspected severe renal insufficiency or severe hepatic disorders.
13. Known or suspected disorders of calcium metabolism associated with hypercalcaemia.
14. 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.
15. Current participation in any other interventional clinical trial.
16. Previously enrolled in this trial.
17. Subjects who have received treatment with any non-marketed drug substance (i.e., an agent which has not yet been made available for clinical use following registration) within a month prior to SV1 or longer, if the class of substance required a longer wash-out as defined above (e.g., biological treatments).
18. Subjects or parent(s) or legal guardian known or suspected of being unlikely to comply with the Clinical Trial Protocol (e.g., alcoholism, drug dependency or psychotic state).

19. Females who are pregnant, or of child-bearing potential and wishing to become pregnant during the trial, or who are breast-feeding.
20. Females of child-bearing potential with positive pregnancy test at SV2.
21. Subject (or their partner) not using an adequate method of contraception according to national requirements.

10.4.2.2 Additional Exclusion Criteria for Subjects Performing HPA Axis Assessments (U.S. Only)

1. A history of serious allergy, allergic asthma or serious allergic skin rash.
2. Known or suspected hypersensitivity to any component of CORTROSYN® (including ACTH/cosyntropin/tetracosactide)
3. Systemic treatment with corticosteroids (including inhaled and nasal steroids) within 12 weeks prior to SV2 or during the trial.
4. Topical treatment with corticosteroids within 2 weeks prior to SV2 or during the trial.
5. Oestrogen therapy (including contraceptives) or any other medication known to affect cortisol levels levels or HPA axis integrity within 4 weeks prior to SV2 or during the trial.
6. Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the trial.
7. Systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole) within 4 weeks prior to SV2 or during the trial. Topical ketoconazole 2 weeks prior to SV2.
8. Hypoglycemic sulfonamides within 4 weeks prior to SV2 or during the trial.
9. Antidepressive medications within 4 weeks prior to SV2 or during the trial.
10. Known or suspected endocrine disorder that may affect the results of the ACTH challenge test.
11. Clinical signs or symptoms of Cushing's disease or Addison's disease.
12. Subjects with diabetes mellitus.
13. Known or suspected cardiac condition.
14. Not following nocturnal sleep patterns.

10.4.2.3 Additional Exclusion Criteria for Subjects *Not* Performing HPA Axis Assessments

1. Topical treatment on the trunk and/or limbs with very potent (WHO group IV) corticosteroids within 2 weeks prior to Visit 1 or during the trial
2. Topical treatment on the face and/or sensitive areas (armpits, groin, under the breasts and in other skin folds around the genitals and buttocks) with potent or very potent (WHO groups III-IV) corticosteroids within 2 weeks prior to Visit 1 or during the trial

10.4.3 Subject Screening Log

All subjects screened for this study will be logged on a screening log. This log will list whether subjects were included or not. If a subject is not enrolled, the main reason will be listed. The list will be prepared according to local regulations about personal data protection.

10.4.4 Subject Registration

At SV1, each subject will be assigned the next (ascending) CRF book number available at the trial site. The CRF book number is a unique subject identifier used throughout the trial, in lieu of the subject's name.

10.5 Withdrawal Criteria

Subjects **may** withdraw for any of the following reasons:

1. *Unacceptable treatment efficacy*: the investigator is free to withdraw the subject at any time for medical reasons.
2. *Unacceptable adverse events*: any adverse event that the investigator or the subject considers unacceptable.
3. *Exclusion criteria*: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
4. *Voluntary withdrawal*: subjects will be free to withdraw from the clinical trial at any time and for any reason.
5. *Other reasons*: other reasons than stated above which requires the subject to (be) withdraw(n) should be specified.

Subjects must be withdrawn if they are found to have become pregnant or experience an allergic reaction to CORTROSYN®.

Subjects who are discovered, after enrolment, not to have fulfilled all in-/exclusion criteria at time of enrolment, should be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, finds withdrawal inappropriate. The final efficacy assessment (at the correct scheduled time) should, however, be attempted to be completed for all subjects. Such deviation(s) from the (Consolidated) Clinical Study Protocol must be reported to LEO Pharma A/S (and IEC/IRB, as appropriate) and recorded in the Clinical Study Report.

In case of premature withdrawal prior to visit 5, the additional tests scheduled for visit 5 should be done at the end of treatment, with the exception of the 24-hour urine collection. Reason(s) for withdrawal will be recorded in the CRF.

Subjects withdrawn will not be substituted.

10.6 Investigational Products

10.6.1 LEO 80185

Finished product (brand) name (if available)/name investigational product	LEO 80185 gel
Formulation	Gel
Active ingredient name/concentration	Calcipotriol 50 mcg/g (as hydrate) Betamethasone 0.5 mg/g (as dipropionate)
Excipients (not quantitative)	Paraffin, liquid Polyoxypropylene-15 stearyl ether Castor oil, hydrogenated Butylhydroxytoluene (E321) (added to Polyoxypropylene-15 stearyl ether by the supplier) All-rac-α-tocopherol (added to Paraffin, liquid by the supplier)
Pack size(s)	60 g in 120 ml bottle
Manufacturer's name of bulk medication (IP)	LEO Pharma A/S
Certifier's name of bulk mediation (IP)	LEO Pharma A/S
Supplier's name	LEO Pharma A/S
Manufacturer's name of subject treatment packages	CCI [redacted]
Certifier's name of subject treatment packages	CCI [redacted]

10.6.2 Packaging of Investigational Products

LEO 80185

Individual bottles containing LEO 80185 gel will be dispensed at each visit by the site. The number of bottles dispensed at each visit is dependent on the subject's age and BSA at Visit 1. The individual bottles will be labeled in compliance with national laws and regulations of the participating countries.

Each individual bottle of investigational product will be packed in a separate bottle container. This bottle container serves to protect the bottle from sunlight and must be used for storage of the bottle at all times.

The individual bottle container and individual bottles will be identified by a label in compliance with national laws and regulations of the participating countries.

10.6.3 Storage of Investigational Products

The investigational product, LEO 80185, should be stored in a safe and secure place inaccessible for children. Do not store above 25°C. Do not refrigerate. Keep the bottle in outer carton and away from sunlight.

10.6.4 Administration of Investigational Products

10.6.4.1 LEO 80185

Route of Administration	Topical
Dosing Range (g)	Up to 100 g gel per week
Dosing frequency	Once daily application
Weekly Maximum (g)	Up to 100 g
Time of day for dosing	No specific requirements
Relation of time of dosing to dietary intake	No specific requirements

The investigational product will be dispensed by the (sub)investigator/investigational staff at Visit(s) 1, 2, 3 and 4. The dispenser should ensure that the subject and/or parents/legal guardian is/are familiar with the procedures for administration of the LEO 80185 gel. The subject should be instructed to return all dispensed investigational product at the following visit.

The number of bottles dispensed at each dispensing visit (Visit 1, 2, 3 and 4) is dependent on the subject's age and BSA at Visit 1.

- For subjects aged 12 to 14 years with a BSA $\leq$ 1.3 m^2, the maximum weekly dosage will be 50 g of LEO 80185 gel per week. These subjects will be dispensed 2 bottles at each dispensing visit.

- For subjects aged 12 to 14 years with a BSA > 1.3 m^2 and subjects aged 15 to 16 years, 11 months with a BSA ≤ 1.7 m^2, the maximum weekly dosage will be 75 g of LEO 80185 gel per week. These subjects will be dispensed 3 bottles at each dispensing visit.
- For subjects aged 15 to 16 years, 11 months with a BSA > 1.7 m^2, the maximum weekly dosage will be 100 g of LEO 80185 gel per week. These subjects will be dispensed 4 bottles at each dispensing visit.

At Visit 1, a treatment instruction will be handed over to the subject/parent(s)/legal guardian(s) of the subject. On this sheet, the subject/parent(s)/legal guardian (s) will be instructed how to apply the investigational product.

10.6.5 Precautions/Overdosage

LEO 80185
Overdosage with calcipotriol may be associated with hypercalcaemia. In such cases administration of the investigational product will be stopped and the subject will be withdrawn from the trial. Clinically important hypercalcaemia will be managed at the investigator's discretion with rehydration, biphosphonate administration or according to local instructions. Hypercalcaemia should rapidly subside when treatment is discontinued.

Overdosage with betamethasone dipropionate may result in suppression of the pituitary adrenal function causing secondary adrenal insufficiency which is usually reversible. In such cases symptomatic treatment is indicated. In case of chronic toxicity the corticosteroid therapy must be discontinued gradually.

If severe skin irritation or skin infections develop, LEO 80185 gel should be discontinued and appropriate therapy instituted.

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than by noting any clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

10.6.6 Treatment Assignment

Subjects who have been found to comply with all the protocol's inclusion and exclusion criteria will start treatment and be dispensed investigational product at Visit 1. Each bottle

will have a unique identification number. When a bottle is dispensed to the subject, the unique identification number for that bottle will be recorded in the subject's medical record and the CRF.

10.6.6.1 Randomisation Code List

Not applicable

10.6.6.2 Subject Identification List

The investigator will maintain a list of all subjects included in the trial at the trial site including each subject's identity, date of enrolment and corresponding CRF book number so that any subject may be identified if required for any reason. The list is kept by the investigator and will not be copied to LEO Pharma A/S.

10.6.7 Blinding of the Trial

Not applicable

10.6.8 Breaking the Randomisation Code

Not applicable

10.6.8.1 Un-blinding of Individual Subject Treatment

Not Applicable.

10.6.8.2 Un-blinding of the Clinical Trial

Not Applicable.

10.6.9 Drug Accountability and Compliance Checks

The investigator is fully responsible for the investigational products at the trial site. Dispensing of investigational products may be delegated to, e.g. a hospital pharmacy as locally applicable.

The person responsible for dispensing the investigational products will be responsible for maintaining adequate control of the investigational products and for documenting all transactions with them. Investigational products must be stored in a safe and secure place, and proper dispensing arrangements must be made.

10.6.9.1 Sponsor-Investigator Drug Accountability

All investigational products supplied by the Contract Manufacturing Organisation (CMO) on behalf of LEO Pharma A/S will be returned to the CMO and be fully accounted for by the monitor with the help of the person responsible for dispensing the investigational products. Accountability will be documented by use of drug accountability forms.

Investigational products may be returned from the trial site either to the CMO directly or via the LEO Pharma A/S affiliate/ CRO responsible for the running of the clinical trial.

10.6.9.2 Investigator-Subject Drug Accountability

At each visit, investigational product, including (empty) containers, dispensed at the previous visit must be returned by the subject. An inventory (Individual Drug Accountability Form) will be kept of all investigational product given to and returned by each subject enrolled in the trial. This inventory must be available for inspection during monitoring visits and will be checked by the monitor to ensure correct dispensing of investigational product.

10.6.9.3 End of Trial Drug Accountability

All investigational product supplies returned to the CTS CMO will be reconciled with the Individual Drug Accountability Forms. All returned bottles will subsequently be weighed by the CTS CMO to determine the amount of investigational product used.

10.6.9.4 Treatment Compliance

At all on-treatment visits, the subject will be asked if she/he has used the medication as prescribed. If this is not the case, the degree and nature of non-compliance will be specified.

10.6.10 Prior and Concomitant Treatment

Use of concomitant treatment should be recorded in the subject's medical record and the CRF (treatment/drug name, dose, indication and dates of start and stop).

Use of non-marketed/other investigational products one month prior to SV1 and during the trial is not permitted.

Changes of doses (including starting) of drugs that, while not specifically indicated for treatment of the indication being studied, are known to have an effect (positive or negative) on the indication, are not permitted.

For all subjects, treatments requiring washout before SV2/Visit 1 are listed below, with the required individual washout periods indicated in brackets:

- Topical treatment with corticosteroids (2 weeks prior to SV2)
- Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on scalp or body psoriasis (etanercept) (4 weeks prior to Visit 1), adalimumab, infliximab (2 months prior to Visit 1)*, ustekinumab (4 months prior to Visit 1)* or experimental products (4 weeks/5 half-lives (whichever is longer) prior to Visit 1)
- Systemic treatment with therapies other than biologicals, with a possible effect on scalp or body psoriasis (e.g., retinoids, immunosuppressants, PUVA) within 4 weeks prior to Visit 1
- UVB therapy within 2 weeks prior to Visit 1
- Any topical treatment on the scalp or body (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1
- Systemic calcium, vitamin D supplements, antacids, diuretics, antiepileptics, diphosphonates or calcitonin (4 weeks prior to SV2)

** Note: the time between SV1 and Visit 1 cannot be longer than 8 weeks, and between SV1 and SV2 not longer than 7 weeks, therefore subjects receiving, or having recently received, these treatments at SV1 cannot be enrolled.*

For subjects performing HPA axis assessments, additional treatments requiring washout before SV2/Visit 1 are listed below, with the required individual washout periods indicated in brackets:

- Systemic treatment with corticosteroids (including inhaled and nasal steroids) (12 weeks prior to SV2)*
- Oestrogen therapy (including contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity (4 weeks prior to SV2)
- Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin), systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole), hypoglycaemic sulfonamides, antidepressive medications (4 weeks prior to SV2). Topical ketoconazole (2 weeks prior to SV2).

Treatments which cannot be used during the treatment period (Visits 1-5) are the same as those requiring a washout period, as listed previously, with the addition that the following are not allowed:

- Initiation of, or changes to, concomitant medication that could affect scalp or body psoriasis (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors).
- Excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sunlamps, etc.).

The following concomitant anti-psoriatic treatments are allowed during the trial:

Scalp:	No other treatment allowed. Non-medicated shampoo is allowed.
Trunk/limbs:	No other treatment allowed. Bath oils and moisturizing soaps are allowed.
Face and sensitive areas:	For subjects performing HPA axis assessments: Any topical treatment allowed except corticosteroids. Bath oils and moisturizing soaps are allowed. For subjects *not* performing HPA axis assessments: Any topical treatment allowed except potent or very potent (WHO groups III-IV) corticosteroids. Bath oils and moisturizing soaps are allowed.

Sensitive areas refers to armpits, groin, under the breasts and in other skin folds around the genitals and buttocks.

The maximum amount of topical treatment containing vitamin D analogues (calcipotriol, calcitriol or tacalcitol) is limited to the following including the amount of investigational product used:

- 50 g ointment/gel/cream per week for subjects aged 12 to 14 years with a BSA ≤ 1.3 m^2 .
- 75 g ointment/gel/cream per week for subjects aged 12 to 14 years with a BSA > 1.3 m^2 and subjects aged 15 to 16 years, 11 months with a BSA ≤ 1.7 m^2 .
- 100 g ointment/gel/cream per week for subjects aged 15 to 16 years, 11 months with a BSA > 1.7 m^2.

During the follow-up period, subjects who require a repeat ACTH-challenge test at FU2 should not receive corticosteroid therapy (topical or systemic), enzymatic inductors, cytochrome P450 inhibitors, hypoglycemic sulfonamides, anti-depressive medications, estrogen therapy, or any other medication known to affect cortisol levels/HPA axis integrity. Such subjects should also continue to use contraception if they are of child-bearing potential. Otherwise, there are no restrictions on the use of concomitant treatment during the follow-up period.

10.7 Non-Investigational Medicinal Products

10.7.1 CORTROSYN® (cosyntropin) for injection

CORTROSYN® is a commercial solution for injection containing cosyntropin that will be used for the ACTH-challenge test. One ampoule contains cosyntropin PhEur 250 micrograms (equivalent to 25 IU ACTH).

CORTROSYN® will be sourced by the investigational sites.

CORTROSYN® will be used in accordance with the U.S. Prescribing Information for the marketed product (see Appendix III).

CORTROSYN®

Finished product (brand) name (if available)/name investigational product	CORTROSYN® (cosyntropin) for Injection
Formulation	Sterile lyophilized powder to be reconstituted with 0.9% Sodium Chloride Injection, USP
Active ingredient name/concentration	Cosyntropin (α 1-24 corticotropin); 0.25mg per vial
Excipients	Mannitol, glacial acetic acid and sodium chloride. It contains no antimicrobial preservative.
Pack size(s)	Box of 10 vials of CORTROSYN® (cosyntropin) for Injection
Manufacturer's name	11570 6th Street Rancho Cucamonga, CA 91730, U.S.A.
Supplier's name	Not Applicable.
Certifier's name	11570 6th Street Rancho Cucamonga, CA 91730, U.S.A .

10.7.1.1 Packaging and Labelling

The marketed product, as available in the U.S. will be used for this study without any re-labelling or re-packaging of the product.

10.7.1.2 Storage

CORTROSYN® should be stored in a safe and secure place inaccessible for children. The temperature for storage should be at 15 to 30°C. The Investigator is responsible for ensuring that the storage of CORTROSYN® is in accordance with these conditions. Should there be any evidence that these conditions have not been maintained the product should be destroyed and spoiled stock replaced.

10.7.1.3 Reconstitution and Administration

The contents of one vial (0.25mg of CORTROSYN®) should be reconstituted in 2 to 5ml of 0.9% Sodium Chloride Injection, USP, and injected intravenously over a 2-minute period. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted CORTROSYN® should be used promptly and should not be retained. Any unused portion should be discarded.

The timing of administration of CORTROSYN® during the study is detailed in Section 10.8.4.1.

10.7.1.4 Precautions

Prior to injection of CORTROSYN®, the investigator and staff must be prepared to treat any possible anaphylactic/allergic/hypersensitivity reaction. Severe anaphylactic reactions to CORTROSYN® can be minimised by discontinuing the IV injection at the earliest sign of any local or general reaction such as redness, urticaria, pruritus, flushing of the face, malaise or dyspnoea. In the rare event of a serious allergic/anaphylactic reaction, local procedures should be followed and IM/IV epinephrine (adrenaline), IV high dose corticosteroids, IV antihistamines and intravenous fluids must be readily available and immediately used as appropriate. Protection of the airway must also be considered and managed appropriately. Because of the risk of an allergic reaction, the injections should be given under medical supervision and the subject kept under observation for approximately one hour. If subjects experience an allergic reaction to CORTROSYN® they should be withdrawn from the trial. Repeat administration may increase the risk of hypersensitivity. Subjects should be instructed to inform subsequent physicians of previous use of corticotropic hormones. See the Prescribing Information for CORTROSYN® in Appendix III for further details.

10.7.1.5 Drug Accountability

The investigator is fully responsible for the CORTROSYN® at the trial site. Dispensing of CORTROSYN® may be delegated, e.g. to a hospital pharmacy, as locally applicable.

The person responsible for dispensing the CORTROSYN® will be responsible for maintaining adequate control and for documenting all transactions. All CORTROSYN® sourced locally by the investigator (or designee) will be fully documented by use of (internal) drug accountability forms. An inventory will be kept of all CORTROSYN® dispensed for each subject in the trial. The batch number/lot number and expiry date of the CORTROSYN® dispensed will be recorded. This inventory must be available for inspection at monitoring visits and will be checked to ensure correct dispensing of CORTROSYN®.

10.7.2 0.9% Sodium Chloride Injection, USP

0.9% Sodium Chloride Injection, USP will be sourced by the investigational sites in the U.S. and reimbursed by LEO Pharma A/S. There is no requirement for a specific brand or manufacturer to be used.

0.9% Sodium Chloride Injection, USP will be used in accordance with the product monograph specific to the chosen product.

10.7.2.1 Packaging and Labelling

The marketed product, as available in the U.S. will be used for this study without any re-labelling or re-packaging of the product.

10.7.2.2 Storage

The product should be stored in a safe and secure place inaccessible for children and in accordance with the manufacturer's instructions (e.g. product monograph or labels) specific to the chosen product.

10.7.2.3 Precautions

Product specific precautions and handling instructions will be provided in the product monograph specific to the chosen product.

General precautions for use with 0.9% Sodium Chloride Injection, USP include:

- Do not use unless the solution is clear and seal intact.
- Do not re-use containers
- Discard unused portion

10.7.2.4 Drug Accountability

The investigator is fully responsible for the 0.9% Sodium Chloride Injection, USP at the trial site.

Dispensing of the 0.9% Sodium Chloride Injection, USP may be delegated, e.g. to a hospital pharmacy, as locally applicable. The person responsible for dispensing the 0.9% Sodium Chloride Injection, USP will be responsible for maintaining adequate control and for documenting all transactions. All 0.9% Sodium Chloride Injection, USP sourced locally by the investigator (or designee) will be fully documented by use of (internal) drug accountability forms. An inventory will be kept of all 0.9% Sodium Chloride Injection, USP dispensed for each subject in the trial. The batch number/lot number and expiry date of the 0.9% Sodium Chloride Injection, USP dispensed will be recorded. This inventory must be available for inspection at monitoring visits and will be checked to ensure correct dispensing of the 0.9% Sodium Chloride Injection, USP.

10.8 Trial Procedures

10.8.1 Schedule of Trial Procedures

Visit	**SV1** [1]	**SV2** [1,2]	**1**	**2**	**3**	**4**	**5**[3]	**FU1**[4]	**FU2**[5]
Day	**-56 to -7**	**-7 to -3**	**0**	**14 ± 2**	**28 ± 2**	**42 ± 2**	**56 ± 2**	**+ 14 ± 2**	**+ 28 ± 2**
Informed consent	X								
Demographics	X								
Medical history	X								
Physical examination	X								
Height, weight and BSA	X	X							
Inclusion/exclusion criteria	X	X	X						
Vital signs (blood pressure, heart rate)		X			X		X		
Haematology/biochemistry/ urinalysis [6]		X			X		X	X [7]	
Pharmacokinetic blood sample [8]					X				
ACTH challenge test [9]		X			X		X		X
Instruction for 24-hour urine collection and dietary calcium intake diary	X			X		X			
Review of dietary calcium		X			X		X		
Collection of 24-hour urine [10]		X			X		X		
Urine pregnancy test [11, 12]		X			X		X		
Adverse events		X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
Investigator's assessment of extent of psoriasis (BSA) and extent of scalp psoriasis		X	X						
Investigator 's global assessment of disease severity on the scalp and on the body		X	X	X	X	X	X		

Visit	**SV1** [1]	**SV2** [1,2]	**1**	**2**	**3**	**4**	**5**[3]	**FU1**[4]	**FU2**[5]
Day	**-56 to -7**	**-7 to -3**	**0**	**14 ± 2**	**28 ± 2**	**42 ± 2**	**56 ± 2**	**+ 14 ± 2**	**+ 28 ± 2**
Patient's global assessment of disease severity on the scalp and on the body		X	X	X	X	X	X		
Investigator's assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)		X	X	X	X	X	X		
Patient's assessment of itching and sleep		X	X	X	X	X	X		
Dispensing of IP			X	X	X	X			
Return of IP				X	X	X	X		
IP Compliance				X	X	X	X		

1. There should be at least 4 days between SV1 and SV2 so dietary information (diary) can be collected.
2. It will be acceptable that the following assessments are done on the day prior to the ACTH challenge: vital signs, spot urine collection, pregnancy test, AEs, concomitant medication and assessments of psoriasis
3. In case of early withdrawal prior to visit 5, the additional tests scheduled for visit 5 should be done at the end of treatment, with the exception of the ACTH challenge test and the 24-hour urine collection.
4. Follow-up Visit 1 is only applicable for subjects who at the last on-treatment visit have ongoing (serious or non-serious) adverse event(s) classified as possibly/probably related/not assessable relationship to the investigational product and for subjects with albumin corrected serum calcium *above* reference range at the last on-treatment visit.
5. Applicable only to subjects in the U.S. performing HPA axis assessments. Follow-up Visit 2 is only applicable if serum cortisol is ≤18 mcg/dl at 30 min after the ACTH challenge test at Visit 3 or Visit 5.
6. Blood and spot urine samples should be collected at the end of treatment for subjects who are withdrawn from trial prior to Visit 5.
7. If laboratory results suggest albumin corrected serum calcium *above* reference range at the last on-treatment visit, a follow-up test will be performed.
8. PK sample to be taken prior to the application of investigational product on the day of the visit
9. Applicable only to subjects in the U.S. performing HPA axis assessments. ACTH challenge test should be performed at 8.00 a.m. ± 30 min after checking vital signs and collecting blood and urine samples.
10. It will be acceptable that the 24 hour urine sample is collected up to three days prior to the trial visit.
11. For female subjects of childbearing potential.
12. In case of early withdrawal there will be a pregnancy test if possible at their last on treatment visit.

10.8.2 Subject Eligibility

Subject's eligibility for the clinical trial will be checked according to the inclusion and exclusion criteria at visits specified in the flowchart, cf. 10.8.1. Subjects' demographic details and duration of scalp psoriasis will be recorded.

Concomitant medication and medical history are recorded at SV1 and changes in concomitant medication are recorded at all subsequent visits.

Demographic Data
Demographic data will comprise of:
Date of birth
Sex
Ethnic origin
Race
Skin type

The subjects will self-report their ethnicity (Hispanic or Latino, not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other).

The skin type of the subject will be recorded according to the following classification and can be assessed by the (sub)investigator or research nurse:

Fitzpatrick Skin Type

Skin Type	Skin Colour (unexposed skin)	History (to first 30 to 45 minutes of sun exposure after a winter season of no sun exposure)
I	White	Always burns easily; never tans
II	White	Always burns easily; tans minimally
III	White	Burns moderately; tans gradually (light brown)
IV	White	Burns minimally; always tans well (moderate brown)
V	Brown	Rarely burns; tans profusely (dark brown)
VI	Black	Never burns; deeply pigmented

Height and Weight

The subject's weight (with indoor clothing and without shoes) will be recorded in kg and the height (without shoes) will be recorded in cm.

Duration of psoriasis vulgaris

The duration of psoriasis vulgaris will be recorded to the nearest whole year.

Relevant Medical History, Concomitant Medication and Concurrent Diagnoses

Relevant medical history, concomitant medication and concurrent diagnoses will be recorded.

Physical Examination

Physical examination will consist of: Routine medical examination including gross neurological assessment and other appropriate system.

Vital Signs

Recording of vital signs comprises:

- Heart rate (beats per minute), supine after 5 min rest
- Blood pressure, systolic and diastolic (mmHg), supine after 5 min rest

The same arm will be used for all measurements. The arm (right or left) used for measurement will be recorded in the CRF.

Assessment of vital signs resulting in abnormal values will be repeated in order to exclude an erroneous assessment. Individual results will be classified as "normal", "abnormal with no clinical significance" or "abnormal with clinical significance".

Dietary calcium intake – diary instructions

The (sub)investigator/site staff should perform a review of the subject's normal dietary intake of calcium-rich nutrients – mainly milk and dairy products, but also a high intake of calcium-fortified products. The subject will be instructed to keep a diary of the daily intake of calcium-rich nutrients in the 4-day period prior to SV2 (3 days prior to and during the baseline 24-hour urinary collection).

At SV2, the number of daily servings of dairy (or calcium fortified) products defined as one cup (240 ml) of milk or yoghurt, 1.5 ounces (43 g) of cheese or any calcium-fortified product with a calcium content of 300 mg/cup will be estimated. The subject will be instructed that the number of daily calcium servings should not exceed five. Also the subject should keep the intake of calcium-rich nutrients the same three days prior to and during each subsequent 24-hour urine collection. At the following visit, i.e. Visit 3 and Visit 5 respectively, the (sub)investigator/site staff should review the intake of calcium-rich nutrients with the subject. Based on the diary entries the (sub)investigator/site staff should estimate the number of daily calcium servings for each day and these will be recorded in the CRF.

Instruction on 24-hour urine collection

In addition to the instructions on dietary calcium intake, the (sub)investigator/site staff should instruct the subject on how to perform the 24-hour urine collection. The procedure for collecting a 24 hour urine sample should be for subject to pass their first urine of the day as normal and then to collect all urine passed in the next 24 hours which should include their first urine on the second morning.

10.8.3 Clinical Assessment

10.8.3.1 Investigator Assessments

The (sub)investigator will make the clinical assessments listed below. Ideally, all assessments for a subject should be made by the same (sub)investigator.

Investigator's Global Assessment (IGA) of Disease Severity – Scalp Psoriasis and Body Psoriasis

At SV2 and Visits 1 to 5, and early withdrawal (if applicable), the (sub)investigator will make a global assessment of the disease severity of the scalp psoriasis and body psoriasis (separately) by use of the 5-point scale below. The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

(0) Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
(1) Almost clear	Plaque thickening = none or possible thickening but difficult to ascertain whether there is a slight elevation above normal skin level

Scaling = none or residual surface dryness and scaling
Erythema = light pink coloration

(2) Mild
Plaque thickening = slight but definite elevation
Scaling = fine scales partially or mostly covering lesions
Erythema = light red coloration

(3) Moderate
Plaque thickening = moderate elevation with rounded or sloped edges
Scaling = most lesions at least partially covered
Erythema = definite red coloration

(4) Severe
Plaque thickening = marked or very marked elevation typically with hard or sharp edges
Scaling = non-tenacious or thick tenacious scale, covering most or all of the lesions
Erythema = very bright red coloration; extreme red coloration; or deep red coloration

***Note**: IGA of the scalp should include <u>all</u> scalp psoriasis lesions, defined as those areas of the scalp where there are any signs of redness, thickness or scaliness caused by psoriasis.*

The scalp is defined by the hair line. Parts of scalp psoriasis lesions that extend outside the defined area of the scalp should <u>not</u> be included in the assessments.

At SV2 and Visit 1 the disease severity of scalp psoriasis and the disease severity of body psoriasis must be graded at least as moderate in order to meet the inclusion criteria.

Subjects with disease severity classified as “Clear” or “Almost clear” disease after the treatment period will be rated as having “Controlled disease”.

Investigator’s Assessment of the Extent of Psoriasis Vulgaris
In order to obtain baseline data of psoriatic severity for all the subjects enrolled in the trial, the (sub)investigator will also assess the extent of the subject’s total psoriatic involvement at SV2 and Visit 1.

The total psoriatic involvement (e.g., the arms, the legs, the trunk, the scalp and the face) will be recorded as a percentage of the total BSA, estimating that the surface of the subject’s full, flat palm (including the five fingers) correlates to approximately 1% of the BSA.

Investigator's Assessment of the Extent of Scalp Psoriasis
A baseline assessment of the extent of scalp psoriasis as percentage of the total scalp area will be done at SV2 and Visit 1, estimating that the surface of the subject's full, flat palm (including the five fingers) correlates to approximately 25% of the scalp area.

Investigator's assessment of the extent and severity of clinical signs of psoriasis vulgaris (Redness, Thickness, Scaliness)
At SV2 and Visits 1 to 5 and early withdrawal (if applicable), the (sub) investigator will make assessments of the extent and severity of clinical signs of the subject's psoriasis on specific areas of the body in terms of three clinical signs: redness, thickness and scaliness.

The **extent** of psoriatic involvement will be recorded for each of the four areas: head*, arms**, trunk*** and legs**** using the following scale:

0 = no involvement
1 = < 10%
2 = 10 - 29%
3 = 30 - 49%
4 = 50 - 69%
5 = 70 - 89%
6 = 90 - 100%

*) head includes the neck
**) arms include hands
***) trunk includes flexures
****) legs include buttocks and feet

The **severity** of the psoriatic lesions in each of the four areas will be recorded for each of the signs of redness, thickness and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic lesions on the given body region, will be determined according to the scale below:

Redness

0	=	none (no erythema)
1	=	mild (faint erythema, pink to very light red)
2	=	moderate (definite light red erythema)
3	=	severe (dark red erythema)

4	=	very severe (very dark red erythema)

Thickness

0	=	none (no plaque elevation)
1	=	mild (slight, barely perceptible elevation)
2	=	moderate (definite elevation but not thick)
3	=	severe (definite elevation, thick plaque with sharp edge)
4	=	very severe (very thick plaque with sharp edge)

Scaliness

0	=	none (no scaling)
1	=	mild (sparse, fine-scale lesions, only partially covered)
2	=	moderate (coarser scales, most of lesions covered)
3	=	severe (entire lesion covered with coarse scales)
4	=	very severe (very thick coarse scales, possibly fissured)

PASI is calculated using the formula given below based on the Investigator's assessment of the extent and severity of the disease locally (head, trunk, arms, legs).
The following formula will be used to calculate the PASI:

Head	$0.1 (R + T + S)E = W$
Arms	$0.2 (R + T + S)E = X$
Trunk	$0.3 (R + T + S)E = Y$
Legs	$0.4 (R + T + S)E = Z$

Where: R = score for redness; T = score for thickness; S = score for scaliness; E = score for extent

The sum of $W+X + Y + Z$ gives the total PASI, which can range from 0 to 72.

10.8.3.2 Subject Assessments

The subjects will make the following clinical assessments:

Patient's Global Assessment of Disease Severity – Scalp Psoriasis and Body Psoriasis
At SV2 and Visits 1 to 5, and early withdrawal (if applicable), the subject will make a global assessment of the disease severity of scalp psoriasis and body psoriasis (separately) by use of the 5-point scale below.

The assessment will be based on the condition of the disease at the time of evaluation and not in relation to the condition at a previous visit.

The qualified site staff person will explain the categories of the scale to the subject and the subject will tell the qualified site staff person which category to tick. This assessment must be made prior to the investigator's assessments.

Patient's Global Assessment of Disease Severity Scale

Clear	No psoriasis symptoms at all
Very mild	Very slight psoriasis symptoms, does not interfere with daily life
Mild	Slight psoriasis symptoms, interferes with daily life only occasionally
Moderate	Definite psoriasis symptoms, interferes with daily life frequently
Severe	Intense psoriasis symptoms, interferes or restricts daily life very frequently

***Note**: Subjects with disease severity classified as "Clear" or "Very Mild" disease after the treatment period will be rated as having "Controlled disease".*

Patient's Assessment of Itch and Sleep

At SV2 and Visits 1 to 5 and early withdrawal (if applicable), subjects will complete the itch and sleep questionnaire consisting of three questions (Appendix V). Subjects will be asked to rate the intensity of their itch and sleep loss during the last 24 hours by marking a line on the scale.

10.8.3.3 Imaging Assessments

Not Applicable

10.8.4 Laboratory Assessments

10.8.4.1 Central Analysis

Samples for analysis of the parameters listed below will be taken as scheduled in the flowchart (cf. 10.8.1) or at early withdrawal from the treatment period of the study.

It is recommended that indwelling catheters introduced under topical anaesthesia are used for the repeated blood sampling, to minimise discomfort for the subject, unless the (sub)investigator judges that there are reasons for not doing it.

A 6.5 ml sample of venous blood and a 30 ml spot urine sample will be taken at SV2, Visit 3 and Visit 5. The 6.5 ml sample of blood will consist of 2 ml for haematology analysis, 2.5 ml for serum biochemistry analysis and 2 ml for analysis of plasma parathyroid hormone. The samples will be taken before the ACTH-challenge test that is also scheduled for these visits (for U.S. only). Measurement of serum cortisol concentration will be included in the biochemistry analysis, and this value will be the baseline serum cortisol concentration for the ACTH-challenge test.

At Visit 3, a 12mL (2 x 6 mL) blood sample will be taken for pharmacokinetic analysis.

Prior to SV2, Visit 3 and Visit 5, subjects will collect 24 hour urine. It is allowed to collect the 24-hour urinary sample up to three days prior to the study visit.

The Central Laboratory will provide the materials and instructions necessary for the collection and transport of the samples.

The following analyses will be performed on the blood samples:

Haematology
Haemoglobin
Haematocrit
Red blood cell (RBC) count
Mean corpuscular volume (MCV)
White blood cell (WBC) count, including differential count
Platelet count

Serum/plasma Biochemistry
Cortisol
Urea
Creatinine

Albumin
Sodium
Potassium
Chloride
Calcium
Phosphate
Parathyroid hormone (plasma)

Urinalysis
The following will be analysed quantitatively in the collected 24 hour urine:
Calcium
Phosphate
Creatinine
Volume

The following analyses will be performed on the spot urine sample by dipstick test:
Glucose
Ketones

The laboratory will also report:
Albumin-corrected serum calcium in mmol/l using the formula:
serum calcium (total) in mmol/l + (0.02 x [40-serum albumin in g/l])

For the 24 hour urine sample the following will be calculated:
Total calcium excretion
Total phosphate excretion
Total creatinine excretion
Calcium: creatinine ratio
Phosphate: creatinine ratio

If any laboratory results are abnormal, the (sub)investigator should follow-up the subject as clinically appropriate.

Pharmacokinetic Analysis
A 12 mL (2 x 6mL) blood sample for PK analysis will be collected Visit 3 prior to the application of investigational product on the date of the visit.

A blood sample (2 x 6mL) for pharmacokinetic evaluation will be drawn at Visit 3 (4 weeks of treatment) prior to the application of LEO 80185 on the day of the visit. Validated bioanalytical assays will be used for quantification of calcipotriol, betamethasone dipropionate and the metabolites MC1080 and betamethasone 17-propionate in the plasma sample. Full details for taking, storing and shipping the samples for PK analysis will be provided separately.

ACTH Challenge test

The ACTH-challenge test will be performed at SV2, Visit 3 and Visit 5. If the subject withdraws prior to completing treatment, the ACTH-challenge test should *not* be performed at early withdrawal.

If the result of the ACTH-challenge test at Visit 3 or Visit 5 shows a serum cortisol concentration ≤18 mcg/dl at 30 minutes after the ACTH-challenge, a further ACTH-challenge test is required 28 days later at visit FU2. If the results of the ACTH-challenge test at Visit FU2 continue to show a serum cortisol concentration ≤18mcg/dl at 30 minutes after ACTH-challenge, further ACTH-challenge tests should be performed, but not more often than at 4-weekly intervals, until the adrenal suppression resolves (i.e., serum cortisol concentration >18mcg/dl at 30 minutes after the ACTH-challenge).

The following procedures should be performed prior to the ACTH-challenge tests at SV2 and Visit 3 and 5: Blood pressure/heart rate measurement, blood/urine sampling for central laboratory analysis (haematology/biochemistry/urinalysis) and urine pregnancy test (in female subjects of child-bearing potential).

To perform the ACTH-challenge test, a 2.5 ml sample of venous blood will be drawn at 08.00 a.m. ±30 minutes. This sample is also the one on which the biochemistry analyses are performed, as detailed above. After this, CORTROSYN® is injected, as described in Section 10.7. Two further 2.5 ml samples of venous blood will be drawn exactly 30 and 60 minutes after the injection (counting from the end of the period over which the injection is given). Serum cortisol concentrations will be determined for each blood sample by the Central Laboratory.

The time of injection and of blood sampling will be recorded in the CRF.

The following blood volumes will be drawn per subject performing HPA axis assessments:
6 ml for Haematology;

13.5 ml for Biochemistry
15 ml for ACTH challenge testing
12 ml for PK analysis
Total amount of blood drawn per subject, for central analysis: 46.5 ml

The following blood volumes will be drawn per subject *not* performing HPA axis assessments:
6 ml for Haematology;
13.5 ml for Biochemistry
12 ml for PK analysis
Total amount of blood drawn per subject, for central analysis: 31.5 ml

Follow-up testing:
A 7.5 ml sample will be collected from subjects requiring additional ACTH challenge testing at FU2 if HPA-axis suppression is observed at Visit 3. A 2.5 ml sample will be collected from subjects at FU1 if laboratory results suggest albumin corrected serum calcium above reference range at the last on-treatment visit.

10.8.4.2 Local Analysis

A urine pregnancy test will be performed at the trial site at SV2, Visit 3 and 5, and, if applicable, at FU2, in female subjects of child-bearing potential. The test kits will be provided by the Central Laboratory.

10.8.5 Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (ICH Harmonized Tripartite Guideline for Good Clinical Practice, E6 (R1)).

A Serious Adverse Event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening

- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

  or

- other medically important conditions*)

*) Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are allergic broncospasm, blood dyscrasias and convulsions.

Global Pharmacovigilance, LEO Pharma A/S is responsible for the assessment of headquarter expectedness according to LEO Pharma A/S procedures. The relevant reference document for this clinical trial is Investigator's Brochure, edition 12 and subsequent updates as agreed between the head of Medical Department, and the medical director, Global Pharmacovigilance, LEO Pharma A/S.

At all visits, the subject will be asked a non-leading question by the investigator: "How have you felt since I saw you last?" No specific symptoms will be asked for.

If there are no AEs to record, no further questions will be asked and "NO" should be stated. In case there are one or more AEs to record, "YES" should be stated and the investigator will record the event term, intensity, duration, suspected causal relationship to the investigational product and outcome.

It is important that the investigator also observes the subject for any changes not reported by the subject and records these changes.

Only medically qualified personnel must assess AEs.

10.8.5.1 Reporting of Adverse Events

Events reported by the subject or observed by the (sub)investigator and that fall into any of the above definitions must be recorded on the adverse event page of the CRF and should be described in the following manner:

The **nature** of the event will be described in precise English medical terminology (i.e. not necessarily the exact words used by the subject). Whenever possible, a specific diagnosis should be stated (e.g. allergic contact dermatitis).

For cutaneous adverse events the **location** must be part of the adverse event description and may be described as either the *face, scalp or trunk/limbs*. Additionally, the location will be described using the following terminology:

- *lesional/perilesional* (≤2 cm from the border of lesion(s) treated with investigational product) or
- *distant* (>2 cm from the lesion border)

The **intensity** of the event will be described in terms of mild, moderate or severe according to the investigator's clinical judgement.

- **Mild:** The adverse event does not interfere in a significant manner with the subject's normal functioning level and requires no medical intervention.
- **Moderate:** The adverse event interferes with the subject's normal functioning level and may or may not require medical intervention.
- **Severe:** The adverse event produces significant impairment of the subject's functioning or requires medical intervention.

The **duration** of the event will be reported as the start date and stop date of the event.

The **causal relation** of the event to the use of the investigational product will be described in terms of probable, possible, not related or not assessable according to the following:

Probably related

- Follows a reasonable temporal sequence from administration of the investigational product
- Could not be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product
- Disappears or decreases on cessation or reduction in dose of the investigational product
- Reappears or worsens upon re-challenge

Possibly related

- Follows a reasonable temporal sequence from administration of the investigational product

- Could also be reasonably explained by the subject's clinical state, environmental or toxic factors or other therapies administered to the subject
- Follows a known pattern of response to the investigational product

Not related

- Does not follow a reasonable temporal sequence from administration of the investigational product
- Is better explained by other factors like the subject's clinical state, environmental or toxic factors or other therapies administered to the subject
- Does not follow a known pattern of response to the investigational product

Not assessable

- The adverse event cannot yet be judged otherwise because present information is insufficient or contradictory. A final assessment (i.e. probably, possibly or not related) shall be made as more information becomes available, at the latest when the subject has completed the trial.

The **outcome** of the event will be classified and handled as follows:

Recovered/resolved	The event has stopped. The stop date of the event must be recorded.
Recovering/resolving	The subject is clearly recovering from an event. The event is, however, not yet completely resolved. Follow-up on the event is required until final outcome is established.
Not recovered/not resolved	Event is still ongoing. Follow-up on the event is required until final outcome is established.
Recovered with sequelae	The event has reached a state where no further changes are expected and the residual symptoms are assumed to persist. An example is hemiparesis after stroke. The stop date of the event must be recorded.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the adverse event.

Unknown	Unknown to investigator, e.g. subject lost to follow-up.

Once a subject has completed the clinical trial, the investigator should follow up for outcome on all non-serious adverse events classified as possibly/probably related to the investigational product or not assessable for 14 ± 2 or until final outcome is determined, whichever comes first.

10.8.5.2 Other Events to Be Reported

Pregnancy

Pregnancy which occurs during a clinical trial with an investigational product must be reported to LEO Pharma A/S within one calendar day of first knowledge using the Pregnancy Follow-up Form supplied by LEO Pharma A/S. All pregnancies must be followed up until delivery or termination.

Please also confer with chapter 10.5, withdrawal criteria.

Overdose

Any overdose defined as any higher dose than prescribed for the individual subject must be reported on the adverse event form of the CRF book. AEs originating in the overdose must be documented on a separate line.

Aggravation of condition

Any clinically significant aggravation/exacerbation/worsening of the initially treated condition compared to baseline, judged by an overall medical assessment, must be reported as an AE.

10.8.6 Serious Adverse Events

10.8.6.1 Reporting of Serious Adverse Events

Any Serious Adverse Event (SAE), related or unrelated to the investigational product or any trial procedure after signature of the Informed Consent Form must be reported to LEO Pharma A/S on the (paper) **Serious Adverse Event Form – Clinical Trial** within **24 hours**.

Note: Planned hospitalisation or planned prolonged hospitalisation do not fulfil the criteria for being an SAE. The elective nature of the event must be clearly documented in the subject's medical record.

SAEs must be reported on the adverse event form of the CRF book. Additionally reports must be made using the paper Serious Adverse Event Form – Clinical Trial, supplied by LEO Pharma A/S. Apart from the assessment of the intensity, causal relationship to the investigational product(s) and/or trial procedures, the action taken and the outcome to date, this report must contain a comprehensive narrative description of the course of the event.

The completed Serious Adverse Event Form – Clinical Trial must be faxed or scanned and e-mailed to the following local LEO Pharma A/S affiliates:

For sites in Australia and New Zealand:

LEO Pharma Pty Ltd: Fax: +61 7 3250 1299 email: drug.safetyau@leo-pharma.com

For sites in Canada:

LEO Pharma Inc.: Fax: +1 905 886 6639 email: drug.safety.ca@leo-pharma.com

For sites in France:

LEO Pharma: Fax: + 33 1 30144613 email: pharmacovigilance.fr@leo-pharma.com

For sites in Germany:

LEO Pharma GmbH: Fax: +49 6102 201 100 email: drug.safety.de@leo-pharma.com

For sites in the United Kingdom:

LEO Pharma: Fax: +44 1844 276385 email: ukdrug.safety@leo-pharma.com

For sites in the U.S.:

LEO Pharma Inc.: Fax: +1 973 637 8398 email: usdrugsafety@leo-pharma.com

All other relevant reports of diagnostic procedures, hospital records, autopsy reports etc. must be included, as applicable or upon request from Global Pharmacovigilance.

The IRB(s)/IEC(s), regulatory authorities and concerned investigators will be notified of SAEs according to current regulation and local requirements.

All Suspected, Unexpected Serious Adverse Reactions (SUSARs) are subject to expedited reporting to regulatory authorities.

SAEs must be followed indefinitely until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial.

10.8.7 Source Data

Source data: *All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).* (ICH E6, 1.51).

Source documents: *Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).* (ICH E6, 1.52).

Source Data Verification (SDV) is a key function in assuring the sponsor that clinical trial information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will, during the conduct of the clinical trial, perform SDV to confirm the accuracy and completeness of CRFs by verifying selected (as specified below) data recorded in the CRF against data recorded in source documents to ensure such records are consistent.

To enable SDV, it is essential that what constitutes source data/documents (see definition above) for the clinical trial data to be collected in the CRF as well as where such data can be found at the trial site is established and agreed with the investigator at each trial site and documented prior to initiation of the clinical trial.

Source data cannot be entered directly into the CRF. Source data should as a general rule be recorded in the subject's medical record or other defined document normally used at the trial site. Source data may be entered on a worksheet only if the clinical trial requires capture of data, which are normally not part of the subject's medical record.

For this clinical trial, the following parameters collected in the CRF should be verifiable from source documents available at the trial site:

- Date of trial visits and date leaving the clinical trial
- Relevant medical history and diagnosis

- Nature of contraception used by the subject and result of pregnancy test(s), when applicable
- Data for evaluation of eligibility criteria
- Dispensation/administration of investigational product
- Concomitant medication (including changes) and diagnoses
- Subject demographics (sex, date of birth)
- Adverse events, (nature, dates)

In addition to the above, the following should be added to the subject's medical record in chronological order, i.e. when these are allocated to the subject:

- Date(s) of conducting the informed consent process including date of provision of subject information
- Date of enrolment
- CRF book number
- The fact that the subject is participating in a clinical trial in psoriasis with a treatment arm of calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g gel for up to 8 weeks.

After un-blinding the clinical trial, the investigators will be notified of the actual treatment allocation and be asked to record this in the subject's medical record.

10.9 Safety Evaluation

10.9.1 Primary Response Criteria

- Adverse drug reactions (ADRs)
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 and at Week 8
- Change in albumin-corrected serum calcium from baseline (SV2) to Week 4, Week 8, and end of treatment
- Change in 24-hour urinary calcium excretion from baseline (SV2) to Week 4, Week 8, and end of treatment

10.9.2 Secondary Response Criteria

- Adverse events (AEs)
- Subjects with serum cortisol concentration of ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4 and at Week 8

- Change in urinary calcium:creatinine ratio from baseline (SV2) to Week 4 and Week 8

10.9.3 Evaluation of (Serious) Adverse Events

Refer to Section 10.9.1 and 10.9.2.

10.9.4 Evaluation of Laboratory Data

Refer to Section 10.9.1. and 10.9.2.

10.9.5 Evaluation of Other Observations

- PK evaluation

10.10 Efficacy Evaluation

10.10.1 Secondary Response Criteria

- Subjects with “Controlled disease” (i.e., “Clear” or “Almost clear”) according to the investigator’s global assessment of disease severity on the body at end of treatment.
- Percentage change in PASI from baseline to end of treatment.
- Subjects with “Controlled disease” (i.e., “Clear” or “Very mild”) according to the patient’s global assessment of disease severity on the body at end of treatment.

10.11 Statistical Analysis

10.11.1 Subject Qualification for Analysis

All subjects enrolled into the trial (i.e., signed informed consent obtained and a CRF number assigned) will be accounted for in the clinical study report.

All subjects who apply any IP will be included in the full analysis set and analysed for efficacy. Exclusion from the full analysis set will be carefully considered for subjects who apply no IP or who provide no efficacy data following start of treatment.

All subjects who apply any IP and for whom the presence or confirmed absence of adverse events is available will be included in the safety analysis set and analysed for safety, except the analysis of the results from the ACTH-challenge test.

For the analysis of the results from the ACTH-challenge test a per protocol analysis set will be defined by including the subjects performing HPA axis assessments from the full analysis set, however excluding the subjects who do not:

- apply any IP

- meet the inclusion criterion concerning evidence of adrenal function at baseline
- provide any results for the ACTH-challenge test after receiving IP

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the clinical study report.

10.11.2 Reasons for Leaving the Trial

The reasons for leaving the trial will be presented separately for subjects who apply any IP and for enrolled subjects not assigned to treatment.

10.11.3 Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects in the safety analysis set and per protocol analysis set as these are the datasets used for primary response criteria.

Demographics include age, sex, ethnicity, race and skin type. Other baseline characteristics include duration of psoriasis vulgaris, physical examination, investigator's global assessment of disease severity on body, PASI (calculated from the investigator's assessment of extent and severity of the clinical signs) , investigator's assessment of extent of psoriasis (BSA and scalp) , patient's global assessment of disease severity on body, concomitant medication and concurrent diagnoses.

Age and sex will also be presented by centre.

10.11.4 Compliance

Compliance with treatment instructions will be tabulated for all subjects who apply any IP.

The number and percentage of subjects who comply and who do not comply with the trial treatment regimen will be summarised. The extent of non-compliance as categories of the percentage of applications missed (e.g. ≤ 10%, > 10 to 20%, etc.) will also be presented.

10.11.5 Analysis of Safety

The analysis of safety will be based on the safety analysis set according to the defined response criteria, except the analysis of the results from the ACTH-challenge test which will be based on the per protocol analysis set.

10.11.5.1 Adverse Events

Adverse events will be coded in accordance with the current version of the MedDRA dictionary.

All adverse events recorded during the course of the trial will be included in the subject data listings. An event will be considered emergent with the trial treatment if it started after the first application of the investigational product or if it started before this and increased in intensity after the first application of investigational product. The tabulations described below will only include the events that are emergent with the trial treatment.

The number of subjects experiencing each type of adverse event (according to MedDRA Preferred Terms within Primary System Organ Class) will be tabulated regardless of the number of times each adverse event is reported by each subject.

An overview summary of the number of subjects with any adverse events, adverse drug reactions, lesional/perilesional adverse events, serious adverse events and adverse events leading to withdrawal from the trial will be produced.

The causal relationship to IP for each type of adverse event (according to the Preferred Term) will be tabulated. Where there are several recordings of causal relationship to IP for a given type of adverse event, causal relationship will be taken as the most-related recording from the last report of that adverse event, since that is when the investigator will be in possession of most information and so best able to judge causal relationship.

The intensity for each type of adverse event (according to the Preferred Term) will be presented. Where there are several recordings of intensity for a given type of adverse event the most severe intensity will be selected.

Adverse drug reactions are defined as adverse events for which the investigator has not described the causal relationship to IP as “not related”. The number of subjects experiencing each type of adverse drug reaction (according to the Preferred Term) will be tabulated. The intensity for each type of adverse drug reaction will be presented.

The number of subjects experiencing each type of lesional/perilesional adverse event, lesional/perilesional adverse event on the body and lesional/perilesional adverse event on the scalp (according to the Preferred Term) will be tabulated.

Serious adverse events and adverse events leading to withdrawal from the trial will be evaluated separately, and a narrative for each will be given.

10.11.5.2 ACTH-Challenge Test

The following percentages will be calculated:

- Percentage of subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 and at Week 8.
- Percentage of subjects with a serum cortisol concentration ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4 and at Week 8.

The serum cortisol concentration at time 0 (just before the ACTH challenge) and at 30 and 60 minutes after ACTH-challenge at baseline (SV2), Week 4 and Week 8, respectively, will be summarised for the per protocol analysis set.

The serum cortisol concentration at time 0 (just before the ACTH challenge) and at 30 and 60 minutes after ACTH-challenge and also the change in serum cortisol from time 0 to 30 minutes and 60 minutes recorded at baseline (SV2), Week 4, Week 8 and FU2 respectively, will be listed for each subject with a value ≤18 mcg/dl at either 30 or 60 minutes after ACTH-challenge for the per protocol analysis set. Values ≤ 18 mcg/dl at 30 or 60 minutes after ACTH-challenge will be flagged.

10.11.5.3 Exposure

The duration of exposure (weeks) and extent of exposure (subject-treatment-weeks) to IP will be summarised.

10.11.5.4 Drug Accountability

The amount of IP used (g) and the average weekly amount of IP used (g) will be summarized for three different treatment periods (first four weeks, second four weeks and the total treatment period).

10.11.5.5 Laboratory Examinations

For the haematology, biochemistry and urinalysis parameters except the urinary glucose and ketones, the absolute value by visit and the change from baseline (SV2) to Week 4 and Week 8 will be summarised. In addition, the values will be categorised as “low”, “normal” or “high” depending on whether they are below, within or above the laboratory reference range, respectively. Shift tables will be produced showing the categories at baseline (SV2) against those at Week 4 and Week 8.

For the urinary calcium:creatinine ratio, the 95% confidence interval of mean change from baseline to Week 4 and Week 8 will also be presented.

For the albumin-corrected serum calcium and 24-hour urinary calcium excretion, the end of treatment values and the change from baseline to end of treatment will also be summarised and the 95% confidence interval of mean change from baseline to Week 4 and Week 8 and end of treatment will be presented. For these two parameters the end of treatment category will also be included in the shift tables.

The albumin-corrected serum calcium and 24-hour urinary calcium will be listed by visit for all subjects with any of these values out of reference range at any visit. Values outside the reference range will be flagged.

For the urinary glucose and ketones, the values will be categorised by visit as absent or present. Shift tables will be produced showing the presence/absence at baseline (SV2) against presence/absence at Week 4 and Week 8.

The 24-hour urinary calcium excretion will be presented also for the subjects with complete urinary collection. A 24-hour urinary collection is considered incomplete if it is either reported to be incomplete by the subject or if the creatinine excretion is below 0.1 mmol per kg body weight as proposed by Remer et al (32).

10.11.5.6 Other Observations

PK evaluation

The plasma concentrations above the lower limit of quantification will be presented.

Vital signs

For systolic and diastolic blood pressure and heart rate, the absolute value by visit and change from baseline (SV2) to Week 4 and Week 8 will be summarised.

Clinically significant abnormalities in the vital signs at baseline (SV2), Week 4 and/or Week 8 will be presented. Any abnormalities at Week 4 and/or Week 8 that were not present at baseline will be highlighted.

10.11.6 Analysis of Efficacy

The statistical analysis of efficacy will be based on the full analysis set according to the defined response criteria.

The percentage of subjects who achieve “Controlled disease” according to the investigator’s global assessment of disease severity on the body will be presented by visit and at end of treatment. The 95% confidence interval (CI) which is based on a binomial distribution will be presented for the proportion of subjects with “Controlled disease” at end of treatment.

The percentage of subjects who achieve “Controlled disease” according to the investigator’s global assessment of disease severity on the body at end of treatment will also be tabulated by age-group, sex, centre and baseline disease severity according to the investigator’s assessment of body psoriasis.

The percentage change in PASI from baseline to each visit and to end of treatment will be summarised. The 95% CI for mean percentage change in PASI based on a normal distribution will be calculated for end of treatment.

The percentage of subjects who achieve “Controlled disease” according to the patient’s global assessment of disease severity on the body will be presented by visit and at end of treatment. The 95% CI based on a binomial distribution will be calculated for the proportion of subjects with “Controlled disease” at end of treatment.

The percentage of subjects who achieve “Controlled disease” according to the investigator’s global assessment of disease severity on the scalp will be presented by visit and at end of treatment.

The percentage of subjects who achieve “Controlled disease” according to the patient’s global assessment of disease severity on the scalp will be presented by visit and at end of treatment.

The investigator’s global assessment of disease severity on the body and on the scalp, PASI and patient’s global assessment of disease severity on the body and on the scalp will be summarised by visit and at end of treatment.

Patient’s assessment of itching and sleep will be summarised by visit and at end of treatment. In addition, the change from baseline to each visit and end of treatment will be summarised.

10.11.7 General Principles

Categorical data will be summarised using the number and percentage of subjects in each category. Continuous data will be summarised using the mean, standard deviation (SD), median, minimum and maximum values.

All confidence intervals will be two-sided and presented with 95% degree of confidence, unless otherwise stated.

The data recorded during the course of the trial will be presented in individual data listings, according to ICH E3.

For tabulations on changes from baseline, baseline will be defined as the last assessment performed before application of IP.

The end of treatment value for a particular parameter will be defined as the last value recorded for that parameter up to and including Visit 5 (Week 8). However, for laboratory parameters this will be the last value recorded after baseline (SV2) up to and including Visit 5.

All efficacy data will be tabulated by visit using an observed cases approach (i.e. involving only those subjects who attended each specific visit) except for the tabulation of end of treatment values.

All laboratory data will be tabulated by visit using an observed cases approach except for the tabulation of end of treatment values which will be presented for the primary response criteria.

10.12 Trial Committees

LEO 80185 gel has obtained marketing authorisation in 2008 and has been marketed in the U.S., several European countries and more than 40 other countries worldwide, including Canada and Australia. The clinical trial programme for LEO 80185 gel has so far included more than 6000 psoriasis patients, of whom more than 3000 were treated with LEO 80185 gel. LEO 80185 gel has since launch in 2008 to December 2012, been prescribed for approximately 4.8 million treatment courses.

Two non-controlled trials, MBL 0801 and MBL 0412 INT, in adolescent subjects (aged 12-17 years) with psoriasis on the scalp have recently been completed. In a total of 109 adolescent subjects using up to 69 g/week, LEO gel was safe and effective in the treatment of psoriasis vulgaris on the scalp. The effects on calcium metabolism were investigated; no cases of hypercalcaemia and no clinically relevant changes in urinary calcium were reported. The adrenal response to ACTH challenge was assessed in a subset of 30 patients; one patient showed a decrease in cortisol response to ACTH challenge after 4 weeks of treatment which was considered mild (7) (8).

In this trial, patients 12-14 years with a BSA of ≤ 1.3 m^2 will receive up to 50 g/week. Patients 12-14 years with a BSA > 1.3 m^2 and patients 15-16 years, 11 months with a BSA ≤ 1.7 m^2 will receive up to 75 g/week. Patients 15-16 years, 11 months with a BSA > 1.7 m^2 will receive up to 100 g/week. The maximum approved dose in adults is 100g/week.

The use of CORTROSYN® in this trial will be entirely in keeping with the licensed conditions for use as described in the U.S. Prescribing Information, therefore its use in this trial is also not expected to reveal any new safety findings.

It is hence not considered necessary to have a Data Monitoring Committee for this trial.

10.13 Quality Assurance/Audit

LEO Pharma A/S has implemented a system of quality assurance, including all elements described in this protocol. Within this system company Standard Operating Procedures (SOPs) are implemented to ensure that clinical trials are conducted in compliance with regulatory requirements and Good Clinical Practice (GCP). Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by LEO Pharma A/S or inspection by competent authorities.

Any aspect of the clinical trial may be subject to audit by LEO Pharma A/S and/or inspection by regulatory authorities (national or foreign) or IEC/IRB. Such audits/inspections may take place at the sponsor's site(s) or at any trial site including laboratories, pharmacies etc.

The monitor will, in case of audit, announce this in advance to the (sub)investigator and be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

10.13.1 Trial Monitoring

LEO Pharma A/S, as sponsor of this clinical trial, is responsible to the regulatory authorities for assuring the proper conduct of the clinical trial with regard to protocol adherence and validity of the data recorded in the CRFs. The company has therefore assigned persons to monitor this trial. Their duties are to serve as the principal link between (sub)investigators and

LEO Pharma A/S and advise the investigator on the collection and maintenance of accurate, complete, legible, well organised and easily retrievable data for the clinical trial. In addition, they will explain to the investigators any aspect of the (conduct of the) clinical trial, including interpretation of the protocol, the purpose of collecting the specified data and reporting responsibilities.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections (see above) will need direct access to primary subject data, e.g. medical records, laboratory reports, appointment books etc. Because this affects the subject's confidentiality, this fact is included on the Subject Information Sheet and Informed Consent Form.

This clinical trial is organised by LEO Pharma A/S and all enquiries should be made to a member of LEO Pharma A/S staff (see section [6.3], LEO Pharma A/S Personnel).

10.14 Case Report Form Books and Data Handling

10.14.1 Case Report Forms (CRFs)

In this clinical trial data will be collected by means of Remote Data Capture (RDC). The investigator or staff authorised by the investigator will enter subject data into electronic CRFs designed by LEO Pharma A/S. A uniquely numbered CRF book will be used for each subject enrolled. Data recorded in the electronic CRFs will be accessible to site staff through a secure internet connection immediately after entry. The CRFs must be maintained in an up-to-date condition at all times by the investigator.

The investigator, or sub-investigator(s) authorised by the investigator, will electronically sign all sections of CRFs used. This signature information (incl. date of signature) will be kept in the audit trail and cannot be altered. Only medically qualified (sub)investigators can sign data on clinical assessments/safety. Any correction(s) made by the investigator or authorised site staff to the CRF after original entry will be documented in the audit trail. Changes to data already approved, requires the re-signature of the investigator or authorised staff. The person making the change and the date, time and reason for the change will be identified in the audit trail.

The trial monitor will check the CRFs for accuracy and completeness and perform source data verification preferably no later than eight weeks after each subject visit. For archiving purposes each investigator will be supplied with a copy of the CRFs, for all subjects enrolled

at the trial site, via an electronic medium at completion of the trial. Audit trail information will be included. CRFs will be available for inspection by authorised representatives from LEO Pharma A/S (e.g. audit by the quality assurance department), from regulatory authorities and/or IEC/IRBs.

10.14.2 Data Handling

Subject data should be entered into the electronic CRF in a timely manner by authorised site staff. Data will be entered by site staff and systematic data validation will be performed through the discrepancy management system within the data collection software. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the study data manager. All queries, whether generated by the system or by a user, will be in an electronic format. This systematic validation will ensure that a clean and consistent database is provided prior to the statistical analysis being performed.

10.15 Protocol Amendments

Neither the investigator(s) nor LEO Pharma A/S will change the Clinical Study Protocol without written agreement between LEO Pharma A/S and the international co-ordinating investigator. Any modification considered substantial requires approval/favourable opinion by the appropriate regulatory authority and IEC/IRB.

Protocol amendments are issued as Consolidated Clinical Study Protocols comprising all current amendments. Consolidated Clinical Study Protocols become effective when written approval has been provided by the international co-ordinating investigator, the head of Medical Department and the head of Biostatistics and Data Management, LEO Pharma A/S, and approval/favourable opinion from regulatory authorities and/or IEC/IRB has been obtained, as required.

Alternatively, a protocol addendum may be issued to comply with national/regional specific requirements. A protocol addendum becomes effective when written approval has been provided by the international co-ordinating investigator, the head of Medical Department and the head of Biostatistics and Data Management, LEO Pharma A/S, and the and approval/favourable opinion from the relevant regulatory authorities and/or IEC/IRB has been obtained, as required.

10.16 Completion of Trial

10.16.1 Trial Completion Procedures

End of trial should be defined. In most cases this will be the date of the last subject's last visit in each participating country and overall (all countries).

Investigators will be informed when subject recruitment is to cease.

Trial enrolment will be stopped at a trial site when the total requested number of subjects for the clinical trial has been obtained, irrespective of the specific site's planned inclusion number.

Upon completion of the clinical trial, LEO Pharma A/S will undertake arrangements for collection and disposal of any unused trial material that the investigator is not required to keep in his/her files.

LEO Pharma A/S may stop the clinical trial prematurely after consultation with the international co-ordinating investigator, e.g. if the subject recruitment is so slow that the clinical trial cannot be completed within a reasonable time frame. Such premature termination/suspension of the trial will be notified to regulatory authorities and IECs/IRBs, as required.

10.16.2 Provision for Subject Care Following Trial Completion

After the completion of the trial, the subjects will be treated at the investigator's discretion or referred to other physician(s) according to standard practice.

10.16.3 Archiving of Trial Documents

The investigator at each trial site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until LEO Pharma A/S informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for the archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from regulatory authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of the required storage period.

At present according to ICH Guideline:

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. ***It is the responsibility of the Sponsor to inform the investiga-tor/institution as to when these documents no longer need to be retained****.* (ICH E6, 4.9.5)

11 Use of information

This Clinical Study Protocol as well as all other information, data and results relating to this clinical trial and/or to the investigational product(s) is confidential information of LEO Pharma A/S and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO Pharma A/S may use any and all information, data and results from this clinical trial in connection with the development of the investigational product(s) and, therefore, may disclose and/or transfer information, data and/or results to other investigators, regulatory authorities and/or commercial partners.

12 Publication

Basic information of this clinical trial will be posted on the website: www.clinicaltrials.gov before the first subject enters into the clinical trial.

This clinical trial is a multi-centre clinical trial, and publication by an investigator of his/her trial results shall not be made before the first multi-centre publication is made public. Such multi-centre publication will be prepared in collaboration between LEO Pharma A/S and the members of a writing committee, which shall be appointed by LEO Pharma A/S.

If there is no multi-centre publication within eighteen (18) months after the clinical trial has been completed or terminated at all trial sites and all data has been received, defined as data base lock of the clinical trial, the investigator shall have the right to publish the results from the clinical trial generated by the investigator, subject to the following notice requirements.

Prior to submitting or presenting a manuscript relating to the clinical trial to a publisher, reviewer or other outside person, the investigator shall provide to LEO Pharma A/S a copy of all such manuscripts, and LEO Pharma A/S shall have rights to review and comment. Upon the request of LEO Pharma A/S the investigator shall remove any confidential information (other than results generated by the investigator) prior to submitting or presenting the manuscripts. The investigator shall, upon the request of LEO Pharma A/S, delay the publication or presentation to allow LEO Pharma A/S to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still on-going and has not been made public at the time of notification, LEO Pharma A/S and the Writing Committee may also delay the publication or presentation if the manuscript is deemed to harm the ongoing multi-centre publication.

In case of publications made by the investigator after the first multi-centre publication has been published, the above-mentioned requirements must be followed.

LEO Pharma A/S also subscribes to the joint position of the innovative pharmaceutical industry (41) for public disclosure of clinical trial results in a free, publicly accessible database, irregardless of outcome.

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Appendix I

English translation of the Danish Data Protection Agency's terms and conditions for the processing of clinical trial data by medical companies

English translation of the Danish Data Protection Agency's terms and conditions for the processing of clinical trial data by medical companies[1]

Listed below please find an English version of the general terms and conditions, set by the Danish Data Protection Agency, in cases involving authorisation for the processing of sensitive data by medical companies conducting continuous clinical trials of medical products. Circumstances may warrant some variation in the terms and conditions in concrete cases.

AUTHORISATION to process personal data

The Data Protection Agency hereby grants authorisation for processing of personal data for the purpose of the Company's continuous clinical trials, cf. section 50(1)(i) of the Danish Act on Processing of Personal Data. In this connection, the Data Protection Agency lays down the following terms:

General terms

Period of validity: The authorisation is valid until further notice.

1. LEO Pharma A/S - hereinafter called the "Company" is responsible for compliance with these present terms.
2. The data may be used for the sole purpose of performing clinical trials.
3. The Company shall once a year to the Data Protection Agency submit an overview of new, commenced trials as well as a corresponding overview of which trials have been completed in the past year. The overview shall contain as a minimum a title of the trial and name and address of the clinically responsible investigator.
4. Processing of personal data must be performed only by the controller or at the instance of the controller and at his responsibility. It is the responsibility of the controller that compliance of the terms is always observed when data are processed.
5. Any person processing personal data must be cognizant of these present terms.
6. The terms must be complied with also where processing is made by a data processor.

[1] Source: Letter dated 07-Mar-2003 from the Danish Data Protection Agency (Datatilsynet) to the Danish Association of Pharmaceutical Industries (LIF)

7. Facilities used for storage and processing of the data must be organized and fitted up in order to prevent unauthorized access.
8. Data processing must be organized in such a manner that data are protected against accidental or unlawful destruction, loss or impairment. Furthermore, the necessary control should be exercised to ensure that no inaccurate or misleading data are processed. Inaccurate or misleading data or data processed in contravention of the above Act or of these terms shall be rectified or erased.
9. Data must not be kept in a form that makes it possible to identify the data subject for a longer period than is necessary for the implementation of the project.
10. If results from the clinical trial are published this must be done so that it is impossible to identify individual persons.
11. It is a condition that compliance is made with related terms, if any, laid down in accordance with other legislation.

Electronic data

12. Identification data must be encrypted or replaced by a code number or the like. Alternatively, all data can be stored encrypted. Encryption keys, code keys etc. must be stored securely and separate from the personal data.
13. Access to project data can be obtained only through the use of a confidential password. A password must be replaced at least once a year and when conditions dictate it.
14. If personal data are transferred over the Internet or other external network, the necessary security measures must be taken to ensure that the data do not come to the knowledge of any unauthorized third parties. As a minimum, the data must be encrypted during transmission. Transmission of sensitive personal data requires strong encryption. When using internal networks, it must be ensured that unauthorized persons are unable to obtain access to the data.
15. Removable storage media, safety copies of data etc. must be stored securely and under lock and so that unauthorized access is prevented.

Manual data

16. Manual clinical trial materials, including print-outs, failure lists and control lists etc., as well as other material which may directly or indirectly be linked with specific persons, must be stored securely under lock and so that unauthorized access is prevented.

Bio-bank and biological material

17. Samples with biological material and biological material in bio-banks must be stored securely under lock so that unauthorized access is prevented and in such a manner that it is ensured that the material is not lost, impaired or accidentally or illegally destroyed.
18. Biological material marked with civil registration number or name must be stored subject to special safety requirements.
19. The Company shall lay down internal guidelines for storage of biological material relative to the individual trials, and guidelines for storage of biological material in bio-banks. The guidelines shall be updated at least once a year.

Information to be provided to the data subject (trial subject)

20. Where the personal data are to be obtained from the trial subject (through interviews, questionnaires, clinical or para-clinical examination, treatment, observation etc.), detailed data about the project shall be distributed/forwarded to the trial subject. The trial subject must be informed of the name of the controller, the purpose of the project and of the fact that it is voluntary to participate and that consent may be withdrawn at any time. Where the data are to be disclosed to be used for other scientific or statistical purposes, the trial subject shall be advised also of the purpose of the disclosure and identity of recipients, if applicable.

    The data subject should furthermore be advised that the project is notified to the Data Protection Agency in accordance with Act on Processing of Personal Data, and that the Agency has laid down specific terms to be complied with for the project for the purpose of protecting the data subject's privacy.

Disclosure of data

21. Disclosure of data identifying individuals to a third party may take place for other statistical or scientific purposes only.
22. Disclosure may be made only subject to prior approval of the Data Protection Agency. The Data Protection Agency may lay down new terms for the disclosure as well as the recipient's data processing.

    Disclosure of data may, however, take place in accordance with the below-mentioned authorisation to disclose data.

Right of access to personal data

23. The subject of the trial i.e. the data subject has no right of access to the data being processed concerning himself, cf. Section 32(4) of the Act on Processing of Personal Data. This Act does not prevent the grant of access.

Processing by a data processor

24. The Data Protection Agency's conditions shall apply also to processing by a data processor.

25. When data are processed by a data processor, a written agreement shall be made between the controller and the data processor. The agreement shall stipulate that the data processor acts on behalf of the controller only and that the data must not be used for the data processor's own purposes. The controller shall furthermore request sufficient data from the data processor to ensure that the Data Protection Agency's terms can and will be complied with.

26. Where the data processor is established in another Member State it shall, furthermore, appear from the agreement that such other regulations on safety measures with regard to data processors that may be in force in the Member State in question, shall apply also to the data processor in question.

Erasure of data

27. Data in the individual trials shall be erased, made anonymous or destroyed no later than at the expiry of the storage period stipulated by the GCP-rules. It must not subsequently be possible to identify individuals participating in the trial.

28. Alternatively, the data may be transferred for further storage in archive in accordance with the rules of the archive legislation

29. Erasure of data from electronic media shall take place in such a manner that it is impossible to recover the data.

Transfer of data to third countries

30. Transfer of data to third countries, including for the purpose of processing by a data processor, requires the Data Protection Agency's prior approval.

    Transfer may take place in accordance with the below-mentioned transfer authorisation.

31. Transfer may, however, take place without approval of the Data Protection Agency if the data subject has given his explicit consent. The data subject can withdraw his consent.

32. Transfer of data shall take place by courier or registered mail. In case of electronic transmission the necessary security measures shall be taken to prevent unauthorized access. As a minimum, the data must be safely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.

Changes of the notified data processing

33. The Data Protection Agency shall prior to implementation be notified of significant changes to the data processing (in the form of a change to an existing notification). Less significant changes may be notified to the Data Protection Agency subsequently, however not later than four (4) weeks after the implementation.

Discontinuance of notified data processing

34. The Company shall notify the Data Protection Agency immediately if the company discontin-ues carrying out the notified data processing.

AUTHORISATION to disclose data

In connection with its notification the Company has applied for authorisation to disclose data.

The Company has applied for authorisation to disclose data to relevant national and international health and medicines authorities in connection with an application for marketing authorization.

Furthermore, the Company has applied for authorisation to disclose data concerning adverse events to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.

The Data Protection Agency hereby grants authorisation to the disclosure, cf. Section 10(3) of Act on Processing of Personal Data.

The authorisation in granted on the following terms:

Period of validity: The authorisation is valid until further notice.

1. The relevant data may be disclosed to national and international health and medicines authorities in connection with an application for marketing authorization; to national and international health and medicines authorities according to national and international law on reporting of adverse events in clinical trials.
2. Only data required in the specific situation concerned may be disclosed.
3. The data may be disclosed to the recipient only in a form that does not identify individual persons. It must thus not be possible for the recipient on the basis of the received data alone to identify the persons related to the data.
4. The Company shall at any time be able to verify to the Data Protection Agency which transfers of data have been made.

AUTHORISATION to transfer personal data to third countries

In connection with its notification the Company has applied for authorisation to transfer personal data to third countries. The company wishes to transfer data for the purpose of data processing to be carried out by named data processors in third countries.

Furthermore, the Company wishes to transfer data to health and medicines authorities in third countries to comply with these countries' law on reporting of adverse events in clinical trials and in connection with applications for a marketing authorization.

According to Section 50(2) of Act on Processing of Personal Data, transfer of sensitive data to third countries can take place with the authorisation of the Data Protection Agency. According to section 50 (5), the Data Protection Agency may lay down more detailed conditions for the carrying out of the processing operations for reasons of protection of the privacy of the data subject in question.

The Data Protection Agency hereby grants authorisation to transfer data to third countries, cf. Section 50(2) of Act on Processing of Personal Data.

The authorisation is granted on the following terms:

Period of validity: The grant is valid until further notice.

1. Data may be transferred for processing by data processors with whom the Company has an agreement on data processing, and to health and medicines authorities in third countries in order to comply with the law of these countries on reporting of adverse events in clinical trials and in connection with an application for marketing authorization.
2. When data are transferred to and from third countries the necessary safety measurements must be taken to ensure that the data are not abused and to prevent unauthorized access. The data shall be delivered personally or sent by courier or registered post. Electronic transmission of data may take place only if the data are securely encrypted during the entire transmission. Transfer of sensitive personal data requires strong encryption.
3. Transfer of data to third countries takes place at the responsibility of the Company. The Company must therefore in each individual case assess whether the relevant transfer can take place, especially in consideration of the recipient's data safety. If it is assessed that the level of protection at the recipient's place is not adequate, transfer is not allowed.
4. The Company shall be able at any time to verify to the Data Protection Agency to which third countries data have been transferred and the purpose of this.

The following terms furthermore apply to transfer to data processors in third countries.

5. Processing of the data must take place only at the instance of the Company and at the Company's responsibility.
6. The Company shall always be in a position to notify the Data Protection Agency of the data processor's name and address.
7. Prior to any transfer of data a written agreement shall be made with the recipient to the effect that the Data Protection Agency's conditions for processing of the data in Denmark shall be complied with when the data processor processes the data.
8. As responsible for the processing, the Company shall obtain information sufficient to ensure that the terms of the Data Protection Agency are complied with.
9. When the data are no longer to be processed by the data processor they must be erased or returned to the Company.

The terms of the Data Protection Agency are valid until further notice. The Data Protection Agency reserves the right to take up the terms for revisions at a later date, if required.

Appendix II

Declaration of Helsinki last amended Seoul 2008

Policy

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another ap-propriately qualified individual must then seek the potential subject's freely-given in-formed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized repre-sentative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
33. The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
34. Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
35. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
36. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

37. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

Appendix III

U.S. Prescribing Information for CORTROSYN® (cosyntronin) for injection

CORTROSYN®™
FOR DIAGNOSTIC USE ONLY
(cosyntropin) for Injection

DESCRIPTION

CORTROSYN™ (cosyntropin) for Injection is a sterile lyophilized powder in vials containing 0.25 mg of CORTROSYN™ and 10 mg of mannitol to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection, USP. Administration is by intravenous or intramuscular injection. Cosyntropin is α 1 - 24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1 - 24 compound is as follows:

Ser	Tyr	Ser	Met	Glu	His	Phe	Arg	Trp	Gly	Lys	Pro	Val	Gly	Lys	Lys	Arg	Arg	Pro	Val	Lys	Val	Tyr	Pro
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24

CLINICAL PHARMACOLOGY

CORTROSYN™ (cosyntropin) for Injection exhibits the full cortico-steroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1 - 20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residues. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of CORTROSYN™ is similar to that of purified natural ACTH. It has been established that 0.25 mg of CORTROSYN™ will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of CORTROSYN™ will produce maximal secretion of 17-OH corticosteroids, 17- ketosteroids and / or 17 - ketogenic steroids.

The extra-adrenal effects which natural ACTH and CORTROSYN™ have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22-39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic poly-peptides containing 1-19 or fewer amino acids have no detectable immunologic activity. Those containing 1-26, 1-24 or 1-23 amino acids have very little immunologic although full biologic activity. This property of CORTROSYN™ assumes added importance in view of the known antigenicity of natural ACTH.

INDICATIONS AND USAGE

CORTROSYN™ (cosyntropin) for Injection is intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency. Because of its rapid effect on the adrenal cortex it may be utilized to perform a 30-minute test of adrenal function (plasma cortisol response) as an office or outpatient procedure, using only 2 venipunctures (see DOSAGE AND ADMINISTRATION section).

Severe hypofunction of the pituitary - adrenal axis is usually associated with subnormal plasma cortisol values but a low basal level is not per se evidence of adrenal insufficiency and does not suffice to make the diagnosis. Many patients with proven insufficiency will have normal basal levels and will develop signs of insufficiency only when stressed. For this reason a criterion which should be used in establishing the diagnosis is the failure to respond to adequate corticotropin stimulation. When presumptive adrenal insufficiency is diagnosed by a subnormal CORTROSYN™ test, further studies are indicated to determine if it is primary or secondary.

Primary adrenal insufficiency (Addison's disease) is the result of an intrinsic disease process, such as tuberculosis within the gland. The production of adrenocortical hormones is deficient despite high ACTH levels (feedback mechanism). Secondary or relative insufficiency arises as the result of defective production of ACTH leading in turn to disuse atrophy of the adrenal cortex. It is commonly seen, for example, as result of corticosteroid therapy, Sheehan's syndrome and pituitary tumors or ablation.

The differentiation of both types is based on the premise that a primarily defective gland cannot be stimulated by ACTH whereas a secondarily defective gland is potentially functional and will respond to adequate stimulation with ACTH. Patients selected for further study as the result of a subnormal CORTROSYN™ test should be given a 3 or 4 day course of treatment with Repository Corticotropin Injection USP and then retested. Suggested doses are 40 USP units twice daily for 4 days or 60 USP units twice daily for 3 days. Under these conditions little or no increase in plasma cortisol levels will be seen in Addison's disease whereas higher or even normal levels will be seen in cases with secondary adrenal insufficiency.

CONTRAINDICATION

The only contraindication to CORTROSYN™ (cosyntropin) for Injec-tion is a history of a previous adverse reaction to it.

PRECAUTIONS

General

CORTROSYN™ (cosyntropin) for Injection exhibits slight immunologic activity, does not contain animal protein and is therefore less risky to use than natural ACTH. Patients known to be sensitized to natural ACTH with markedly positive skin tests will, with few exceptions, re-act negatively when tested intradermally with CORTROSYN™. Most patients with a history of a previous hypersensitivity reaction to natural ACTH or a pre-existing allergic disease will tolerate CORTROSYN™. Despite this however, CORTROSYN™ is not completely devoid of immunologic activity and hypersensitivity reactions including rare anaphylaxis are possible. Therefore, the physician should be pre-pared, prior to injection, to treat any possible acute hypersensitivity reaction.

Drug Interactions

Corticotropin may accentuate the electrolyte loss associated with diuretic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility. A study in rats noted inhibition of reproductive function like natural ACTH.

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with CORTROSYN™ (cosyntropin) for Injection. It is also not known whether CORTROSYN™ can cause fetal harm when ad-ministered to a pregnant woman or can affect reproduction capacity. CORTROSYN™ should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CORTROSYN™ (cosyntropin) for Injection is administered to a nursing woman.

Pediatric Use

(See DOSAGE AND ADMINISTRATION section.)

ADVERSE REACTIONS

Since CORTROSYN®™ (cosyntropin) for Injection is intended for diagnostic and not therapeutic use, adverse reactions other than a rare hypersensitivity reaction are not anticipated. A rare hypersensitivity reaction usually associated with a pre-existing allergic disease and/or a previous reaction to natural ACTH is possible. Symptoms may include slight whealing with splotchy erythema at the injection site. There have been rare reports of anaphylactic reaction. The following adverse reactions have been reported in patients after the administration of CORTROSYN®™ and the association has been neither confirmed nor refuted:

- bradycardia
- tachycardia
- hypertension
- peripheral edema
- rash

DOSAGE AND ADMINISTRATION

CORTROSYN™ (cosyntropin) for Injection may be administered intramuscularly or as a direct intravenous injection when used as a rapid screening test of adrenal function. It may also be given as an intravenous infusion over a 4 to 8 hour period to provide a greater stimulus to the adrenal glands. Doses of CORTROSYN™ 0.25 to 0.75 mg have been used in clinical studies and a maximal response noted with the smallest dose.

A suggested method for a rapid screening test of adrenal function has been described by Wood and Associates (1). A control blood sample of 6 to 7 ml is collected in a heparinized tube. Reconstitute 0.25 mg of CORTROSYN™ with 1mL of 0.9% Sodium Chloride Injection, USP and inject intramuscularly. The reconstituted drug product should be inspected visually for particulate matter and discoloration prior to injection. Reconstituted CORTROSYN™ should not be retained. In the pediatric population, aged 2 years or less, a dose of 0.125 mg will often suffice. A second blood sample is collected exactly 30 minutes later. Both blood samples should be refrigerated until sent to the laboratory for determination of the plasma cortisol response by some appropriate method. If it is not possible to send them to the laboratory or perform the fluorimetric procedure within 12 hours, then the plasma should be separated and refrigerated or frozen according to need.

Two alternative methods of administration are intravenous injection and infusion. CORTROSYN™ can be injected intravenously in 2 to 5 mL of saline over a 2-minute period. When given as an intravenous infusion: CORTROSYN™, 0.25 mg may be added to glucose

or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6-hour period. It should not be added to blood or plasma as it is apt to be inactivated by enzymes. Adrenal response may be measured in the usual manner by determining urinary steroid excretion before and after treatment or by measuring plasma cortisol levels before and at the end of the infusion. The latter is preferable because the urinary steroid excretion does not always accurately reflect the adrenal or plasma cortisol response to ACTH.

The usual normal response in most cases is an approximate doubling of the basal level, provided that the basal level does not exceed the normal range. Patients receiving cortisone, hydrocortisone or spironolactone should omit their pre-test doses on the day selected for testing. Patients taking inadvertent doses of cortisone or hydrocortisone on the test day and patients taking spironolactone or women taking drugs which contain estrogen may exhibit abnormally high basal plasma cortisol levels.

A paradoxical response may be noted in the cortisone or hydrocortisone group as seen in a decrease in plasma cortisol values following a stimulating dose of CORTROSYN™.
In the spironolactone or estrogen group only a normal incremental response is to be expected. Many patients with normal adrenal function, however, do not respond to the expected degree so that the following criteria have been established to denote a normal response:

1. The control plasma cortisol level should exceed 5 micrograms/100 ml.
2. The 30-minute level should show an increment of at least 7 micrograms/100 ml above the basal level.
3. The 30-minute level should exceed 18 micrograms/100 ml. Comparable figures have been reported by Greig and co-workers

Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of CORTROSYN™ and some prefer the 60-minute interval for testing for this reason. While it is true that the 60-minute values are usually higher than the 30-minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period. If the 60-minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value.

In patients with a raised plasma bilirubin or in patients where the plasma contains free hemoglobin, falsely high fluorescence measurements will result. The test may be performed at any time during the day but because of the physiological diurnal variation of plasma cortisol the criteria listed by Wood cannot apply. It has been shown that basal plasma cortisol levels

and the post CORTROSYN™ increment exhibit diurnal changes. However, the 30-minute plasma cortisol level remains unchanged throughout the day so that only this single criterion should be used (3).

Parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit. Reconstituted CORTROSYN™ should not be retained.

HOW SUPPLIED

Box of 10 vials of CORTROSYN®™ (cosyntropin) for Injection 0.25 mg
NDC # 0548-5900-00

Storage

Store at 15-30°C (59-86°F).

CORTROSYN™ is intended as a single dose injection and contains no antimicrobial preservative. Any unused portion should be discarded.

Rx only

REFERENCES

1. Wood, J.B. et al. LANCET 1.243, 1965.
2. Greig, W.R. et al. J. ENDOCR 34.411, 1966.
3. McGill, P.E. et al. ANN RHEUM DIS 26.123, 1967.

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Appendix IV

WHO Classification of Corticosteroids

WHO CLASSIFICATION OF TOPICAL CORTICOSTEROIDS

Based on the Anatomical Therapeutic Chemical (ATC) classification system

Group I: weak	Hydrocortisone Methylprednisolone Prednisolone
Group II: moderately potent	Alclometasone Clobetasone Desonide Flumetasone Fluocortin butyl Fluprednidene Hydrocortisone butyrate Triamcinolone
Group III: potent	Amcinonide Beclometasone Betamethasone Betamethasone dipropionate Budesonide Desoximetasone Diflorasone Diflucortolone Fluclorolone acetonide Fludroxycortide Fluocinolone acetonide Fluocinonide Fluocortolone Fluticasone Halometasone Mometasone Prednicarbate Ulobetasol
Group IV: very potent	Clobetasol Halcinonide

Appendix V

Itch and Sleep Questionnaire

Itch and Sleep Questionnaire

Subject CRF Number _____

Visit _____

Date _____

Please rate the intensity of your maximal itching on your scalp during the last 24 hours

No itch_____Worst possible

Please rate the intensity of your maximal itching on your body (upper limbs, trunk and lower limbs) during the last 24 hours

No itch_____Worst possible

Please rate your sleep loss during the last 24 hours

No sleep loss_____Worst possible

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