Consolidated Clinical Trial Protocol

Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to < 17 Years) with Plaque Psoriasis

A phase 2 trial evaluating the safety and efficacy of once daily topical treatment with LEO 90100 aerosol foam in adolescent subjects with plaque psoriasis

An international, multi-centre, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent subjects with plaque psoriasis

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

LEO Pharma A/S	**Trial ID:**	**LP0053-1108**
	Date:	**29-AUG-2016**
	Version:	**5.0**

This document has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of participants and named persons associated with the trial as well as to retain commercial confidential information.
Summary data are included but data on individual participants, including data listings, are removed. This may result in page numbers not being consecutively numbered.
Access to anonymised data on an individual participant may be obtained upon approval of a research proposal by the Patient and Scientific Review Board.
Appendices to the clinical trial report are omitted.
Further details and principles for anonymisation is available in the document LEO PHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA

1 Clinical Trial Protocol Statement

1.1 Approval Statement LEO Pharma A/S

The following persons have approved this clinical trial protocol by using electronic signatures as presented on the last page of this document:

PPD

Biostatistics Lead, Skin Inflammation

PPD

Medical Lead, Skin Inflammation

1.2 Approval Statement International Coordinating Investigator

The international coordinating investigator approves the clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by manually signing the International Coordinating Investigator Clinical Trial Protocol Approval Form, which is a separate document adjoined to this document.

The following person has approved this clinical trial protocol:

Marieke Seyger, MD, PhD

International coordinating investigator

1.3 Acknowledgement Statement Investigator(s)

Each participating investigator must agree to the approved clinical trial protocol and consolidated clinical trial protocol(s) comprising any subsequent amendment(s) by signing a Clinical Trial Protocol Acknowledgement Form.

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2 Trial Identification

EudraCT number: 2015-000839-33

IND number: 114063. All participating sites will conduct the trial under the IND.

ClinicalTrials.gov Number: NCT02387853

3 Introduction and Rationale

3.1 Psoriasis Vulgaris (plaque psoriasis)

Psoriasis is an immunologic disease that predominantly affects the skin and has a prevalence of approximately 2%, affecting any age (1,2), even though the prevalence of psoriasis in children is lower than in adults (3). The hallmark of psoriasis is inflammation of the skin. In the majority of subjects, psoriasis manifests as plaque type psoriasis, clinically seen as sharply demarcated, elevated, scaling, erythematous plaques located predominantly on the scalp, extensor sides of elbows and knees, and the sacral region (4,5,6). The presentation can sometimes be somewhat different in children, often with scalp involvement (7). Skin lesions can be painful, pruritic and may cause significant emotional and physical discomfort (8,9).

The majority of affected subjects has mild to moderate disease and can be treated with topical therapies (9). In the group of subjects with moderate to severe psoriasis topical therapies are also appropriate either as adjunct to phototherapy, systemic or biologic agents (10,11). One of the advantages of topical therapies is a reduced risk of systemic toxicity compared to other treatment modalities. The most commonly used topical therapies in adults are corticosteroids and vitamin D analogues used either alone or in combination (12).

The fixed combination of calcipotriol 50 mcg/g (as monohydrate) and betamethasone 0.5 mg/g (as dipropionate) in an ointment and gel/topical suspension formulation for body and scalp have already been marketed for several years in adults. These products are marketed in the US under the trade name Taclonex® and in Europe under trade names such as Daivobet®, Dovobet® and Xamiol®. FDA has recently granted approvals for the treatment of scalp psoriasis with Taclonex® Topical suspension in adolescent patients aged 12-17 years and treatment of psoriasis vulgaris with Taclonex® Ointment in adolescent patients aged 12-17 years.

Psoriasis is a chronic, recurrent disease, and no cure exists (4). Despite availability of current treatment options, many subjects are not achieving optimal control of their psoriasis. Patient adherence may be the largest barrier to treatment success with topical therapies. The factors that hinder patient adherence include frustration with medication efficacy, messiness and time-consuming and inconvenient application, among others (13).

To address this need, LEO has developed a new formulation of calcipotriol/betamethasone dipropionate (BDP) which was demonstrated to be more effective than Daivobet ® ointment with a similar safety profile in adults, including systemic safety (14). The foam formulation may be cosmetically more acceptable and user friendly than ointment and therefore potentially lead to better adherence.

3.2 Experience with Investigational Product

LEO 90100 aerosol, foam has been developed to provide a new efficacious product intended for the topical treatment of plaque psoriasis. It contains calcipotriol 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate).

LEO 90100 contains the two drug substances and excipients dissolved in the propellants butane and dimethyl ether (DME) in an aluminium can. At administration a white to off-white foam is formed after evaporation of the propellants. Apart from the propellants, no new excipients have been used in LEO 90100 as compared to Daivobet®ointment.

The individual active components in LEO 90100, i.e. calcipotriol and BDP, are both considered to be well established for topical treatment and their safety profiles are well known, generally well tolerated and with few side effects primarily of mild severity (15).

The propellants used in LEO 90100, butane and DME, are both widely used and are generally regarded as non-toxic and mild or non-irritating. Based on the review of the toxicology data for butane and DME, as well as the non-clinical and clinical studies with LEO 90100, there is no evidence that the use of butane and DME poses any increased risk for adverse events (AEs) of a systemic or local nature.

3.2.1 Clinical experience with LEO 90100

The safety and efficacy of LEO 90100 in the treatment of plaque psoriasis in adults has been evaluated in, a maximum use systemic exposure (MUSE) trial, a vasoconstriction trial, a dermal safety trial, two phase 2 and a pivotal phase 3 trial.

In the three controlled trials evaluating efficacy, LEO 90100, applied once daily for 4 weeks, was shown to be more effective than each of the individual components (calcipotriol and BDP), Daivobet® ointment and the foam vehicle alone in the treatment of psoriasis on the body.

The percentage of subjects in the LEO 90100 group with ‘treatment success’ (‘clear’ or ‘almost clear’) according to the Physician’s Global Assessment of disease severity (PGA) at Week 4 was 45.0% and 54.6% in the phase 2 trials, and 53.3% in the pivotal phase 3 trial.

The effect of LEO 90100 on adrenal function and calcium metabolism in adult subjects has been evaluated in the MUSE trial (16). 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 90100 to lesions on the scalp,trunk and limbs once daily for 4 weeks. The adrenal function was assessed by the Adrenocorticotrophic Hormone (ACTH) -challenge test. There was no indication of an effect on the Hypothalmic-Pituitary-Adrenal (HPA) axis. None of the 35 subjects who completed 28 days of treatment per protocol had a serum cortisol ≤18 mcg/dL 30 minutes after the ACTH stimulation test at Day 28, thus all 35 subjects had an adequate response to the ACTH.

Evaluation of serum and urine markers of calcium homeostastis showed no clinical relevant impact on calcium metabolism after 4 weeks of treatment. A mean amount of 62 g/week (range 14 to 113 g) of LEO 90100 was used during the study.

Overall LEO 90100 was well tolerated, with a low incidence of AEs and a safety profile similar to that of Daivobet® ointment. The most commonly reported adverse effects were the application site reactions irritation and pruritus. The incidence of potentially calcipotriol- or corticosteroid- related AEs was low and in line with previous experience from trials with marketed calcipotriol plus BDP products, and gave no indication of any new concerns.

Further information regarding LEO 90100 relevant to clinical trials can be found in the Investigator's Brochure (IB) (14).

3.3 Trial Rationale

3.3.1 Overall Trial Rationale

To fulfill the pediatric study requirements under the US Pediatric Research Equity Act (PREA), which requires an assessment of the safety and effectiveness of a new dosage form of a drug for the claimed adult indications in all relevant pediatric subpopulations, LEO is committed to conduct a trial with LEO 90100 in adolescent subjects with plaque psoriasis, aged 12 to < 17 years.

The objective of the present phase 2 trial is to evaluate the safety, pharmacodynamics (effect on HPA axis and calcium metabolism) and pharmacokinetics of LEO 90100 in adolescent subjects with plaque psoriasis. Subjects will be treated once daily over a period of 4 weeks.

The trial will be conducted in 100 evaluable adolescent subjects with plaque psoriasis on the body and scalp, to evaluate the safety and effect of LEO 90100 on the calcium metabolism. In a subset of a least 30 subjects treated under maximal use conditions, evaluation of the effect on HPA axis and pharmacokinetics will be performed.

3.3.2 Rationale for safety assessments

To evaluate the safety of the LEO 90100 in this trial, all AEs reported by the subject or observed by the investigator will be recorded. In addition, any effects resulting from systemic absorption of the active components, calcipotriol and BDP, 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 (17). This is due to systemic absorption of the corticosteroid, which then induces suppression of the HPA axis due to a negative feedback effect on the pituitary gland and the hypothalamus (17,18). 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 (19). 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 (18).

In the present study LEO 90100 will be applied to lesions on both body and scalp. The risk of adrenal suppression with LEO 90100 is expected to be low with LEO 90100 being applied under maximal use conditions.

A subset of subjects participating in the study will perform ACTH-challenge test before and after treatment. The pre-treatment test is to ensure that adrenal function is normal before starting the treatment with the investigational product. Serum cortisol concentrations at 30 and 60 minutes after injection will be measured in order to show the maximum cortisol level achieved (18).

Overdosage with topical calcipotriol can cause hypercalcemia (19), due to the systemic absorption of calcipotriol, which then affects calcium metabolism as it is a vitamin D analogue. However, extensive experience with the 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 with a 50 mcg/g concentration). Doses up to 300 g have been used with serum calcium remaining within the normal range (20).

Two studies with calcipotriol ointment have been conducted in children 2-14 years of age and did not show effects on calcium metabolism (21,22). 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 (for subjects undergoing HPA axix testing) and spot urine sampling (for the remaining subjects), as well as measurement of serum calcium, -phosphate, alkaline phosphatase (ALP) and plasma parathyroid hormone (PTH) before, and after treatment.

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 (23). As this study includes adolescents aged 12 to 17 years, some of the subjects may not be in a phase of rapid growth and some subjects might consume large amounts of dairy products. Therefore, there is a possibility of an dietary effect on the calcium excretion.

A review of the subject's normal diet will be done. The subject will be asked to keep a diary of the daily intake of diary products.

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 (24). Hence, patients who cannot stop the use of calcium or vitamin D supplementation > 400 IU/day will be excluded in this study.

Local safety and tolerability will be evaluated, at all visits by a clinical scoring of the signs and symptoms from the application site on a 4-point scale (from absent to severe).

3.3.3 Rationale for efficacy assessment

The present study is primarily designed as a safety study since it is an open label study without a comparator arm. However, the sponsor believes it is important to document any improvements in efficacy in the adolescent population.

Efficacy will be assessed by the PGA on the body and scalp via the physician´s assessment of the extent and severity of clinical signs of plaque psoriasis. Further assessments are outlined in section 8.13 and 8.14.

3.4 Ethical Consideration Statement

The combination product of calcipotriol and BDP has been approved in two formulations (ointment and gel/topical suspension) for use on body and/or scalp psoriasis. LEO 90100 is a new aerosol foam formulation of the well-established fixed combination product of the vitamin D analogue calcipotriol and the potent steroid BDP.

The safety and efficacy of LEO 90100 has been evaluated in two phase 2 and one phase 3 trial. For details see section 3.2 (Experience with Investigational Product) and the IB (14). Side effects are not common in patients using LEO 90100 and serious side effects are uncommon.

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 (25,26,27).

Most topical preparations are greasy and messy to apply, have an unpleasant smell and may cause staining of clothes and fabrics and skin irritation. Patient's compliance is therefore often poor, leading to a bad therapeutic outcome (28). Therefore, there is a need for a patient acceptable topical treatment also in this age group.

If topical treatment is ineffective in adolescents with moderate to severe psoriasis, phototherapy or systemic therapy will be the next step in the treatment. As these treatment modalities have known (systemic) side effects, it is in the interest of the adolescents to find topical treatments with greater adherence and a good safety profile, in order to avoid or postpone systemic treatments.

The safety and efficacy of calcipotriol/BDP combination in other formulations has been investigated in three clinical trials in adolescents aged 12 to 17 years. All three studies contain the elements of systemic safety testing, which would be the main concern for use of these combination products in patients aged 12 to 17 years. Safety information from these three studies and information from off label use indicate a similar safety profile in this population as that seen in adult, with few side effects.

In the present trial, adolescent subjects with plaque psoriasis will be dosed with LEO 90100 for 4 weeks, in alignment with the proposed labeling for adults. The risks associated with prolonged treatment with calcipotriol and potent steroids are well known and will be monitored.

As LEO 90100 contains both calcipotriol and BDP, the same pattern of adverse effects as reported for these individual substances is expected.

For calcipotriol there is an infrequent potential risk of hypercalcemia due to systemic absorption. Based on experience from other formulations (ointment and gel/topical suspension), this risk is minimal when used in the recommended doses. Reports of hypercalcemia with calcipotriol remain uncommon.

For BDP, the most commonly reported adverse events (AEs) are the well-known local class effects for topically applied steroids such as skin atrophy, striae and telangiectasia.

The more serious potential adverse effects are systemic effects such as HPA axis suppression. Clinically significant adrenal insufficiency due to topical corticosteroid treatment is however uncommon in adults and with the data available for LEO 90100 the risk of developing adrenal insufficiency is low under the conditions applied in the present trial (16).

Participation in this trial is voluntary and subjects are allowed to withdraw at any time. 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.

Blood samples will be drawn at scheduled visits during the trial. The expected total blood volume collected is 98 ml for subjects performing HPA axis and PK assessments and 18 ml for subjects not performing these assessments.

Subjects participating in the trial will be under careful supervision by a qualified Investigator during the entire trial period. If any potentially serious reactions are observed, subjects will be withdrawn at the Investigator's discretion or according to withdrawal criteria (Section 7.7).

4 Trial Objectives

4.1 Primary Objective

The primary objective is to evaluate the safety of once daily use of LEO 90100 in adolescent subjects (aged 12 to < 17 years) with plaque psoriasis on the body and scalp.

4.2 Secondary Objectives

The secondary objective is to evaluate the efficacy of once daily use of LEO 90100 in adolescent subjects (aged 12 to < 17 years) with plaque psoriasis on the body and scalp.

5 Trial Endpoints

5.1 Primary Endpoint(s)

- Adverse events (AEs)
- Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4
- Change in albumin-corrected serum calcium from baseline (SV2) to Week4

- Change in calcium excretion from baseline (SV2) to Week 4 in 24-hour urine
- Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in 24-hour urine

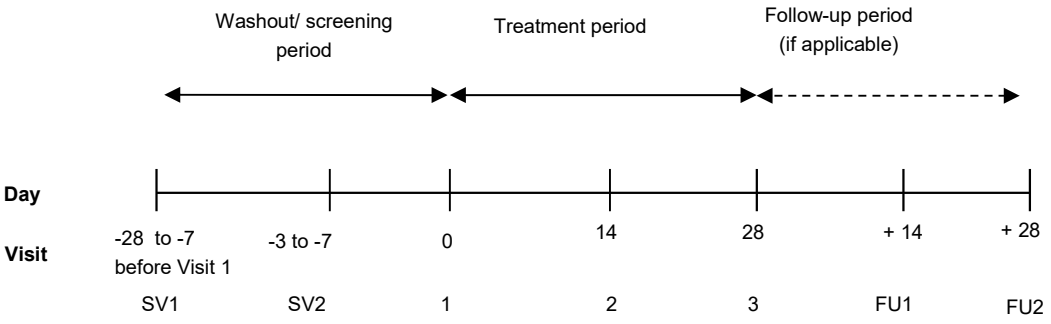
5.2 Secondary Endpoints

- Subjects with serum cortisol concentration of ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4
- Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in spot urine
- Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician´s global assessment of disease severity on the body at Week 4
- Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician´s global assessment of disease severity on the scalp at Week 4
- Percentage change in psoriasis area and severity index (PASI) from baseline (V1) to Week 4
- Subjects with 'treatment success' (i.e., 'clear' or 'very mild') according to the subject´s global assessment of disease severity on the body at Week 4
- Subjects with 'treatment success' (i.e., 'clear' or 'very mild') according to the subject´s global assessment of disease severity on the scalp at Week 4
- Change in itch as assessed by the Visual Analogue Scale (VAS) from baseline (V1) to Week 4

6 Trial Design

6.1 Overall Trial Design

Figure 1: Course of the trial



This will be an international, multi-centre, prospective, open-label , non-controlled, single-group, 4-week trial in adolescent subjects (aged 12 to < 17 years) with plaque psoriasis on the body and scalp.

The subjects will receive topical treatment with LEO 90100 once daily for up to 4 weeks. The trial duration for each subject (including a 4-week washout period) is planned to be 8 weeks and includes 5 visits to the clinic (up to 7 visits if a follow-up visit is required).

Washout/Screening Period

Depending on the prior use of prohibited treatments, the washout/screening period will last for 7 to 28 days prior to the first administration of LEO 90100 (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 3 weeks before SV2; SV2 is performed at 3 to 7 days before Visit 1.

Treatment Period

The treatment period will be 4 weeks and includes 3 visits: Visit 1 (Day 0), Visit 2 (Day 14) and Visit 3 (Day 28). Visits 2-3 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 90100 will be applied once daily to body and scalp psoriasis lesions. Subjects taking part in the HPA axis testing and PK assessments should continue with treatment regardless if their lesions cleared at Visit 2. The remaining 70 subjects, whose psoriasis clears on individual lesions at Visit 2 according to the (sub)investigator, may discontinue treatment but will stay in the trial. 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 in case a Serious Adverse Event (SAE) is ongoing at the last on-treatment visit or if a non-serious adverse event is ongoing with possible/probable/not assessable relationship to the investigational product. 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, 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.

Planned date of enrolment of first subject: Q3 2015
Planned date of completion of last subject: Q1 2017
Estimated number of trial sites and region allocation: approx. 30 sites across North America, Central and Eastern Europe (CEE)

6.2 Sample Size

The sample size was outlined in the Pediatric Study Plan for LEO 90100 and accepted by the FDA as an adequate sample size.

Enrolment of subjects will continue until data from 100 subjects are available for evaluation of the effect of LEO 90100 on calcium metabolism (i.e. the measurement of the serum calcium concentration is available before and at Visit 3). Therefore, the number of enrolled subjects can exceed 100 subjects.

The 100 subjects include the enrolment of 30 evaluable subjects in the assigned sites without adrenal suppression at baseline who undergo an ACTH-challenge test and PK assessments at end of treatment (Visit 3). 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 an ACTH-challenge test and PK assessments. Such subjects will be allowed to complete the trial without an ACTH-challenge test and PK assessments.

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.

The statistical power considerations for this sample size are described in section 11.1.

6.3 Randomisation

Not applicable.

6.4 Blinding

Not applicable.

7 Trial Population and Withdrawal

7.1 Subject Eligibility

The (sub)investigator should only enrol subjects who meet all eligibility criteria, are not put at undue risk by participating in the trial and can be expected to comply with the protocol.

The subject's eligibility for the clinical trial must be checked according to the inclusion and exclusion criteria at visits specified in "Schedule of Trial Procedures" (see section 8.1).

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

7.2 Inclusion Criteria

7.2.1 Inclusion Criteria for All Subjects

1. Signed and dated 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. Adolescent subjects (age 12 to 16 years, 11 months).
3. Either sex.
4. Any race or ethnicity.
5. Plaque psoriasis on trunk and/or limbs affecting at least 2% BSA.
6. Plaque psoriasis on the scalp affecting at least 10% of total scalp area.
7. A total psoriatic involvement on trunk, limbs and scalp not exceeding 30% BSA.
8. PGA score of at least mild on trunk and/or limbs at SV1, SV2 and V1.
9. PGA score of at least mild on scalp at SV1, SV2 and V1.
10. A serum albumin-corrected calcium below the upper reference limit at SV2.
11. Female subjects must be of either
    - non-childbearing potential, i.e. premenarchal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus or has tubal litigation) or,
    - child-bearing potential provided there is a confirmed negative pregnancy test prior to trial treatment to rule out pregnancy.
12. Female subjects of child-bearing potential must be willing to use highly effective contraception at trial entry and until completion. Highly effective contraception is defined as ones which result in a low failure rate (less than 1% per year) as follows:
    - Abstinence (when this is in line with the preferred and usual life style of the subject)
    - Vasectomised partner (given that the subject is monogamous)
    - An intrauterine device
    - Double barrier method defined as two distinct methods (two actual barrier methods, eg. cervical cap and condom)

- Hormonal contraceptive in combination with a barrier method (oral hormonal birth control, oestrogenic vaginal ring, percutaneous contraceptive patches, implants and injectables) for at least one menstrual cycle prior to the pregnancy test at SV2 and must continue using the contraceptive method for at least 1 week after the last application of investigational product

7.2.2 Additional inclusion criteria for subjects undergoing HPA axis testing

13. Plaque psoriasis on trunk and/or limbs affecting at least 10% BSA.
14. Plaque psoriasis on the scalp affecting at least 20% of total scalp area.
15. PGA score of at least moderate on trunk and limbs at SV1, SV2 and V1.
16. PGA score of at least moderate on scalp at SV1, SV2 and V1.
17. Normal HPA axis function at SV2 (serum cortisol concentration above 5 mcg/dl before ACTH challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge).

7.3 Exclusion Criteria

7.3.1 Exclusion Criteria for All Subjects

1. A history of hypersensitivity to any component of LEO 90100.
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 V1 and during the trial:
   a. etanercept – within 4 weeks prior to V1
   b. adalimumab, infliximab – within 2 months prior to V1
   c. ustekinumab – within 4 months prior to V1
   d. experimental products – within 4 weeks/5 half-lives (whichever is longer) prior to V1
3. Systemic treatment with therapies other than biologicals, with a possible effect on scalp and/or body psoriasis (e.g. methotrexate, retinoids, immunosuppressants) within 4 weeks prior to V1 or during the trial.
4. PUVA therapy within 4 weeks prior to V1.
5. UVB therapy within 2 weeks prior to V1 or during the trial.

6. Any topical treatment on the scalp and body including corticosteroids and vitamin D (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to V1 or during the trial.
7. Systemic calcium, vitamin D supplementation > 400 IU/day, antacids, diuretics, antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the trial. (note: stable dose of vitamin D supplementation ≤ 400 IU/day is permitted provided there are no dose adjustments during the study period).
8. Planned initiation of, or changes to, concomitant medication that could affect psoriasis (e.g., betablockers, chloroquine, lithium, ACE inhibitors) during the trial.
9. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis.
10. Subjects with any of the following conditions present on the treatment areas: 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.
11. Other inflammatory skin diseases that may confound the evaluation of scalp and/or body psoriasis.
12. Planned excessive exposure to sun or artificial light sources (including tanning booths etc.) during the trial that may affect scalp and/or body psoriasis.
13. Known or suspected severe renal insufficiency or severe hepatic disorders.
14. Know or suspected disorders of calcium metabolism associated with hypercalcaemia.
15. 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.
16. Current participation in any other interventional clinical trial.
17. Previously treated with LEO 90100 in this trial.
18. 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).
19. In the opinion of the (sub)investigator, 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).

20. Females who are pregnant, or of child-bearing potential and wishing to become pregnant during the trial, or who are breast-feeding.
21. Females of child-bearing potential with positive pregnancy test at SV2.
22. Subject (or their partner) not using an adequate method of contraception according to national requirements.
23. Subjects who are dependant on the trial sponsor or investigator.
24. Subjects afraid of blood withdrawals.

7.3.2 Additional exclusion criteria for subjects undergoing HPA axis testing

25. A history of serious allergy, allergic asthma or serious allergic skin rash.
26. Known or suspected hypersensitivity to any component of CORTROSYN®/Synacthen® (including ACTH/cosyntropin/tetracosactide)
27. Systemic treatment with corticosteroids (including inhaled and nasal steroids) within 12 weeks prior to SV2 or during the trial.
28. 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.
29. Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the trial.
30. Systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole,metronidazole) within 4 weeks prior to SV2 or during the trial. Topical ketoconazole within 2 weeks prior to SV2.
31. Hypoglycemic sulfonamides within 4 weeks prior to SV2 or during the trial.
32. Antidepressive medications within 4 weeks prior to SV2 or during the trial.
33. Known or suspected endocrine disorder that may affect the results of the ACTH challenge test.
34. Clinical signs or symptoms of Cushing's disease or Addison's disease.
35. Subjects with diabetes mellitus.
36. Known or suspected cardiac condition.
37. Not following nocturnal sleep patterns.

7.4 Re-screening of subjects

Re-screening of subjects will be allowed only once, e.g. in case of any abnormal safety lab parameters at the primary screening. Excluded from re-screening are subjects with an HPA axis supression at baseline. Re-screening must be discussed with and approved by the sponsor's medical expert before the screening visit is taking place. The reason for re-screening must be stated in the medical records.

7.5 Subject Enrolment 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.

7.6 Subject Identification List

The (sub)investigator must maintain a list of all subjects randomised/treatment assigned at the trial site including each subject's identity, date of enrolment and corresponding subject identification (ID) so that any subject may be identified if required for any reason. The list is kept by the investigator and must not be copied or retained by LEO or CRO.

At SV1 each subject must be assigned a unique subject ID to protect the subject's identity and which will be used in lieu of the subject's name when the (sub)investigator reports trial-related data.

7.7 Restrictions during Trial

The use of drugs including non-drug therapies and procedures, defined as disallowed in the exclusion criteria, is not permitted during the trial and as also defined in section 8.8.

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

7.8 Withdrawal Criteria

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

1. *Unacceptable treatment efficacy*: the (sub)investigator is free to withdraw the subject at any time based on a medical judgement.
2. *Unacceptable adverse events:* any adverse event that the (sub)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 are free to withdraw from the clinical trial at any time and for any reason. If applicable, the subject's legal representative can withdraw the subject from the trial.
5. *Other reasons:* other reasons than stated above which require 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®/Synacthen®.

Based on the safety profile of LEO 90100, there are no expected risks that would require specific withdrawal criteria in addition to the reasons described above.

Reason(s) for withdrawal must be recorded in the CRF and medical records.

Subjects who are discovered, after enrolment/randomisation, not to have fulfilled all in-/exclusion criteria at the time of enrolment should discontinue treatment unless the (sub)investigator, based on clinical and ethical evaluation, finds discontinuation inappropriate.

In case of premature withdrawal prior to Visit 3, the additional tests scheduled for this visit should be done at the end of treatment, with the exception of the 24-hour urine collection.

For subjects withdrawn from treatment or trial, AEs should be followed up as described in section 9.6.

Subjects withdrawn will not be substituted.

8 Trial Schedule and Assessments

8.1 Schedule of Trial Procedures

Table 1: Schedule of Trial Procedures – Non-HPA Axis Cohort

Note: Separate schedule of trial procedures for subjects in the HPA axis cohort below.

Visit	**SV1** [1)]	**SV2** [1)]	**1**	**2**	**3**	**EW**	**FU1**[2)]
Day	**-28 to -7**	**-7 to -3**	**0**	**14 ± 2**	**28 ± 2**	**--**	**+ 14 ± 2**
Informed consent	X						
Demographics	X						
Medical history and concurrent diagnoses	X						
Physical examination	X				X	X	
Height, weight and BSA [3)]	X		X				
Inclusion/exclusion criteria	X	X	X				
Vital signs (blood pressure, heart rate, oral or ear temperature)		X	X	X	X	X	
25-hydroxy Vitamin D		X					
Haematology/biochemistry/ urinalysis [4)]		X			X	X	X [5)]
Instructions for dietary calcium intake diary	X			X			
Review of dietary calcium		X			X	X	
Urine pregnancy test [6),7)]		X			X	X	
Adverse events		X	X	X	X	X	X
Local safety and tolerability			X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X
Physician´s assessment of extent of psoriasis vulgaris		X	X		X	X	
Physician´s assessment of extent of body psoriasis		X	X		X	X	
Physician´s assessment of extent of scalp psoriasis		X	X		X	X	
Physician´s global assessment of disease severity on the body		X	X	X	X	X	
Physician´s global assessment of disease severity on the scalp		X	X	X	X	X	
Physician´s assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)		X	X	X	X	X	
Subject´s global assessment of disease severity on the body		X	X	X	X	X	
Subject´s global assessment of disease severity on the scalp		X	X	X	X	X	
Subject´s assessment of itch and itch-related sleep loss			X	X	X	X	
CDLQI [8)]			X	X	X	X	
FDLQI [8)]			X		X	X	
Dispensing of IP			X	X			
Return of IP				X	X	X	
IP Compliance				X	X	X	

1) There should be at least 4 days between SV1 and SV2 so dietary information (diary) can be collected.
2) Follow-up Visit 1 is only applicable for subjects who at the last on-treatment visit have an ongoing Serious Adverse Event of any causality or ongoing non-serious adverse event(s) classified as possibly/probably related to the investigational product and for subjects with albumin corrected serum calcium above reference range at the last on-treatment visit.
3) Body surface area (BSA) to be calculated using the Mosteller formula (Appendix 9).
4) Blood and spot urine samples should be collected at the end of treatment for subjects who are withdrawn from trial prior to Visit 3.
5) If laboratory results suggest albumin corrected serum calcium *above* reference range at the last on-treatment visit, a follow-up test will be performed.
6) For female subjects of childbearing potential.
7) In case of early withdrawal there will be a pregnancy test if possible at their last on treatment visit.
8) Ensure the CDLQI and the FDLQI are completed prior to starting any procedures at the visit.

Table 2: Schedule of Trial Procedures – HPA Axis Cohort

Visit	**SV1** [1)]	**SV2** [1),2)]	**1**	**2**	**3**	**EW**	**FU1**[3)]	**FU2**[4)]
Day	**-28 to -7**	**-7 to -3**	**0**	**14 ± 2**	**28 ± 2**	**--**	**+ 14 ± 2**	**+ 28 ± 2**
Informed consent	X							
Demographics	X							
Medical history and concurrent diagnoses	X							
Physical examination	X				X	X		
Height, weight and BSA [5)]	X		X					
Inclusion/exclusion criteria	X	X	X					
Vital signs (blood pressure, heart rate, oral or ear temperature)		X	X	X	X	X		
25-hydroxy Vitamin D		X						
Cortisol (serum)		X			X			
Haematology/biochemistry/ urinalysis [6)]		X			X	X	X [7)]	
Pharmacokinetic sampling [8)]				X	X			
ACTH challenge test [9)]		X			X			X
Instruction for 24-hour urine collection [10)]	X			X				
Instructions for dietary calcium intake diary	X			X				
Review of dietary calcium		X			X	X		
Collection of 24-hour urine [10)]		X			X			
Urine pregnancy test [11), 12)]		X			X	X		X
Adverse events		X	X	X	X	X	X	X
Local safety and tolerability			X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	
Physician´s assessment of extent of psoriasis vulgaris		X	X		X	X		
Physician´s assessment of extent of body psoriasis		X	X		X	X		
Physician´s assessment of extent of scalp psoriasis		X	X		X	X		
Physician´s global assessment of disease severity on the body		X	X	X	X	X		
Physician´s global assessment of disease severity on the scalp		X	X	X	X	X		
Physician´s assessment of the extent and severity of clinical signs of psoriasis vulgaris (for PASI)		X	X	X	X	X		
Subject´s global assessment of disease severity on the body		X	X	X	X	X		
Subject´s global assessment of disease severity on the scalp		X	X	X	X	X		
Subject´s assessment of itch and itch-related sleep loss			X	X	X	X		
CDLQI [13)]			X	X	X	X		
FDLQI [13)]			X		X	X		
Dispensing of IP			X	X				
Return of IP				X	X	X		
IP Compliance				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) Follow-up Visit 1 is only applicable for subjects who at the last on-treatment visit have an ongoing Serious Adverse Event of any causality or ongoing 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.
4) 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.
5) Body surface area (BSA) to be calculated using the Mosteller formula (Appendix 9).
6) Blood and spot urine samples should be collected at the end of treatment for subjects who are withdrawn from trial prior to Visit 3.
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) At Visit 2, a pre-dose trough sample will be taken. At Visit 3, the first PK sample (trough) is taken prior to the ACTH-challenge test. Then following the 30 and 60 minute blood samples for the ACTH-challenge test, the study medication will be applied. Further PK analysis blood samples will be taken at 1, 3 and 5 hours after application of trial medication. A time window of ±10 min relative to the given time points is allowed.
9) 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.
13) Ensure the CDLQI and the FDLQI are completed prior to starting any procedures at the visit.

8.2 Demographics

Demographic data will comprise of:

- Date of Birth, (Only year of birth and age will be collected for EU Countries)
- 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:

Table 3: 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

8.3 Height and Weight

The subject's height must be measured (without shoes) and weight must be determined (in indoor clothing and without shoes).

8.4 Vital Signs

Vital signs must be assessed.

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
- Oral or ear temperature (location to be recorded in the subject's medical record)

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".

8.5 Physical Examination

A physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin in general must be performed.

8.6 Medical History

Relevant medical history and concurrent diagnoses must be recorded:

- Skin history: The duration of plaque psoriasis will be recorded to the nearest whole year.
- Other medical history within the last 12 months.

8.7 Instruction for 24-hour urine collection and dietary calcium intake diary

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 an eDiary of the daily intake of dairy products and calcium-fortified products (e.g. bread, cereals, orange juice or soy milk) in the 4-day period prior to SV2 (3 days prior to and during the baseline 24-hour urinary collection at SV2).

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 spot urine collection (SV2) and during the subsequent 24-hour urine collection (for subjects performing the HPA axis testing). At Visit 3, the (sub)investigator/site staff should review the intake of calcium-rich nutrients with the subject.

Instruction on 24-hour urine collection (only applicable for subjects performing HPA Axis assessment)

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.

8.8 Concomitant Medication

Concomitant medication is defined as any medication used by a subject during the clinical trial apart from the investigational product. Concomitant medication including diagnoses must be recorded.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 and prohibited during the trial are listed below, with the required individual washout periods:

Table 4: Prohibited Medication including Non-Drug Therapies and Procedures (for all subjects)

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
Systemic treatment with biological therapies (marketed or not marketed), with a possible effect on body or scalp psoriasis	Not applicable	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 and any time during the trial treatment phase
Systemic treatment with therapies other than biologicals, with a possible effect on body or scalp psoriasis (e.g., retinoids, immunosuppressants, PUVA)	Body and Scalp	Within 4 weeks prior to visit 1 and any time during the trial treatment phase
UVB therapy within 2 weeks prior to Visit 1	Body and Scalp	Within 2 weeks prior to visit 1 and any time during the trial treatment phase
Any topical treatment on the body or scalp including corticosteroids (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to Visit 1	Body and Scalp	Within 2 weeks prior to visit 1 and any time during the trial treatment phase
Systemic calcium, vitamin D supplementation > 400 IU/day, antacids, diuretics, antiepileptics, diphosphonates or calcitonin Note: Stable doses of oral vitamin D supplementation ≤ 400 IU/day is permitted provided there are no dose adjustments during the study period)	Not applicable	Within 4 weeks prior to visit 1 and any time during the trial treatment phase
Initiation of, or changes to, concomitant medication that could affect body or scalp psoriasis (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors).	Not applicable	Any time during the trial treatment phase
Excessive exposure of treated areas to either natural or artificial sunlight (including tanning booths, sunlamps, etc.).	Body and Scalp	Any time during the trial treatment phase
Note: *The time between SV1 and Visit 1 cannot be longer than 4 weeks, and between SV1 and SV2 not longer than 3 weeks, therefore subjects receiving, or having recently received these treatments at SV1 cannot be enrolled.*		

For subjects performing HPA axis and PK assessments, additional treatments requiring washout before SV2/Visit 1 and prohibited during the trial are listed below, with the required individual washout periods:

Table 5: Prohibited Medication including Non-Drug Therapies and Procedures (for subjects performing HPA axis and PK assessments)

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
Systemic treatment with corticosteroids (including inhaled and nasal steroids)	Not applicable	Within 12 weeks prior to SV2 and any time during the trial treatment phase
Oestrogen therapy (including contraceptives) or any other medication known to affect cortisol levels or HPA axis integrity (4 weeks prior to SV2)	Not applicable	Within 4 weeks prior to SV2 and any time during the trial treatment phase
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).	Body and Scalp	Within 4 weeks prior to SV2 and any time during the trial treatment phase
Topical ketoconazole	Body and Scalp	Within 2 weeks prior to SV2 and any time during the trial treatment phase

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

Table 6: Permitted concomitant anti-psoriatic treatment

Location	Permitted concomitant anti-psoriatic treatment
Scalp	No other treatment allowed. Non-medicated shampoo and conditioners are allowed.
Trunk/limbs	No other treatment allowed. Bath oils and moisturizing soaps are allowed.
Face and sensitive areas	Any topical treatment allowed except corticosteroids or Vitamin D analogues (calcipotriol, calcitriol or tacalcitol). Unlimited use of emollients is allowed. Bath oils and moisturizing soaps are allowed
Note: *sensitive areas refers to armpits, groin, under the breasts and in other skin folds around the genitals and buttocks*	

Follow-up period:

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.

8.9 Pregnancy Test

A urine pregnancy test must be performed at the trial site at SV2, Visit 3 (or on withdrawal from or early completion of the treatment phase of the clinical trial) and, if applicable, at FU2, in female subjects of child-bearing potential. The test kits will be provided by the Central Laboratory.

8.10 Adverse Events

Adverse events must be assessed and recorded as specified in section 9.

8.11 Other Safety Assessments

Not applicable.

8.12 Laboratory Assessments

8.12.1 Safety Laboratory Tests

Samples for analysis of parameters must be taken according to the schedule of trial procedures (section 8.1) or on withdrawal from or early completion of the treatment phase of the clinical trial.

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.

The following analyses will be performed on the blood samples:

Table 7: Planned Safety Analysis

Analyses	Parameter
Haematology	Haemoglobin Haematocrit Red blood cell (RBC) count Mean corpuscular volume (MCV) White blood cell (WBC) count, including differential count Platelet count
Biochemistry (serum/plasma)	Cortisol* Urea Creatinine Albumin Sodium Potassium Chloride Calcium Phosphate Alkaline phosphatase 25-hydroxy vitamin D (SV2 only) Parathyroid hormone (plasma)
* only applicable for subjects performing HPA Axis assessment	

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]

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

Whether an abnormal laboratory finding is considered clinically significant is at the (sub)investigator's discretion. However, all clinically significant abnormalities must be reported as an Adverse Event. For any abnormality which is above/below the predefined alert values, but not considered clinically significant, a written justification should be provided in the subject's medical records and/or the laboratory report (as appropriate).

Handling and shipment instructions are provided in a separate laboratory manual by the central laboratory.

8.12.2 Safety Urinalysis

Samples for analysis of the parameters listed below must be taken as specified in the schedule of trial procedures (section 8.1) or on withdrawal from or early completion of the treatment phase of the clinical trial.

Prior to SV2 and Visit 3, subjects taking part in the HPA axis testing and PK sampling will collect 24 hour urine. It is allowed to collect the 24-hour urinary sample up to three days prior to the study visit.

Table 8: Safety urinalysis

Analyses	Parameter
Urinalysis (will be analysed quantitatively in the collected 24 hour urine) [1)]	Calcium Phosphate Creatinine Volume
spot urine sample:	Glucose[2)] Ketones[2)] Calcium[3)] Phosphate[3)] Creatinine[3)]
[1)] only for subjects performing HPA axis and PK assessments [2)] for all subjects (by dipstick test) [3)] only for subjects *not* performing HPA axis and PK assessments	

For the 24 hour urine and spot urine samples the following will be calculated:

- Total calcium excretion
- Total phosphate excretion
- Total creatinine excretion
- Calcium:creatinine ratio
- Phosphate:creatinine ratio

8.12.3 Pharmacokinetic (PK) Assessments

8.12.3.1 Blood sampling for analysis of LEO 90100 and metabolite(s)

Subjects performing PK assessments will have a pre-dose trough sample taken at Day 14 (Visit 2). At Day 28 (Visit 3), a trough sample will be taken prior to the ACTH-challenge test.

Then following the other blood samples for the ACTH-challenge test, trial medication will be applied and further blood samples for PK analysis will be taken at t = 1 hrs, t = 3 hrs and t = 5 hrs after application. A window of ±10 min for taking blood samples at given time points is allowed. Each PK sample will require 12 ml (2 x 6ml) of blood.

The exact time point of product application and blood sample collection will be noted in the CRF.

Venous puncture should be performed through **untreated areas** of the skin.

A validated bioanalytical assay will be used for simultaneous quantification of calcipotriol, betamethasone dipropionate and the metabolites MC1080 and betamethasone 17-propionate in the plasma samples.

Collection, handling and shipment instructions for pharmacokinetic blood samples are provided in a separate laboratory manual.

8.12.4 Pharmacodynamic (PD) Assessments

ACTH Challenge test

The ACTH-challenge test will be performed at SV2 and Visit 3. 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 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: Blood pressure/heart rate and temperature 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. After this, CORTROSYN® (used in the US)/Synacthen® (used in Europe) 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 blood sampling will be recorded in the CRF.

8.12.5 Total Blood Volume

The following blood volumes will be drawn per subject *not* performing HPA axis and PK assessments:

Table 9: Total blood volume

Sample type	Volume per sample (mL)	Number of samples SV2	Number of samples V3	Total (mL)
Haematology	2	1	1	4
Biochemistry / 25-Hydroxy-Vit D (only SV2)**	5	1	1	10
Parathyroid hormone	2	1	1	4
Total				18

** Note: 25-Hydroxy-Vit D is only tested for at SV2.

The following blood volumes will be drawn for subjects participating in the HPA axis and PK assessments:

Table 10: Total blood volumes for subjects participating in the HPA axis and PK assessments

Sample type	Volume per sample (mL)	Number of samples SV2	Number of samples V2	Number of samples V3	Total (mL)
Haematology	2	1	NA	1	4
Biochemistry / 25-Hydroxy-Vit D (only SV2)**	5	1	NA	1	10
Parathyroid hormone	2	1	NA	1	4
Cortisol (serum)	2.5	1	NA	1	5
Pharmacodynamic	2.5	3	NA	3	15
Pharmacokinetic	12	NA	1	4	60
Total					98

** Note: 25-Hydroxy-Vit D is only tested for at SV2.

Follow-up testing:

If additional blood samples are required, the maximum blood volume to be withdrawn per subject will not exceed the volumes as outlined below:

Table 11: Total blood volumes for follow-up testing

Sample type	Volume per sample (mL)	Number of samples FU1[1)]	Number of samples FU2[2)]	Total (mL)
Haematology	2	1	NA	2
Biochemistry	5	1	NA	5
Parathyroid hormone	2	1	NA	2
Pharmacodynamic	2.5	NA	3	7.5
Total volume				16.5

[1)] FU1: will be collected from subjects at FU1, if laboratory results suggest albumin corrected serum calcium above reference range at the last on-treatment visit.
If haematology and/or PTH results are abnormal and judged by the (sub)investigator as clinically significant at the last on-treatment visit, a 2 ml haematology sample and/or 2 ml PTH sample will be collected at FU1.
[2)] FU2: will be collected from subjects requiring additional ACTH challenge testing at FU2 if HPA-axis suppression is observed at Visit 3.

8.13 Patient Reported Outcomes

The subject's assessments must be made at the very start of the visit, before they are assessed by site staff. The subject must make self-assessments as follows:

Subject´s Global Assessment of Disease Severity – Body Psoriasis and Scalp Psoriasis

At SV2 and Visits 1 to 3, and early withdrawal (if applicable), the subject will make a global assessment of the disease severity of body psoriasis and scalp 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.

Table 12: Subject´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

Subject´s Assessment of Itch

At Visits 1 to 3 and early withdrawal (if applicable), subjects will complete the assessment of itch).

The visual analogue scale (VAS) will be used to assess itch. The horizontal line of the VAS represents the range of itch severity, from 0 (no itch at all) at one end to 10 (worst itch you can imagine) at the other. Subjects will be asked to rate the maximal intensity of itch during the last 24 hours, by putting a single vertical line across the horizontal line at the spot he/she feels best reflects this (Appendix 5).

Subject´s Assessment of Itch-related Sleep Loss

At Visits 1 to 3 and early withdrawal (if applicable), subjects will complete the assessment of itch-related sleep loss.

The VAS will be used to assess itch-related sleep loss. The horizontal line of the VAS represents the range of sleep loss, from 0 (no sleep loss at all) at one end to 10 (worst possible sleep loss). Subjects will be asked to rate the itch-related sleep loss during the last night, by putting a single vertical line across the horizontal line at the spot he/she feels best reflects this (see Appendix 6).

Children’s Dermatology Life Quality Index (CDLQI)

At Visits 1 to 3 and early withdrawal (if applicable), subjects will be asked to complete the CDLQI questionnaire (Appendix 7), which is a validated dermatology specific questionnaire.

The Family Dermatology Life Quality Index (FDLQI)

A family member of the subject will be asked to complete the FDLQI questionnaire (Appendix 8) at visits specified in the schedule of trial procedures (section 8.1).

It is very important that it is the same family member filling in the FDLQI-questionniare throughout the study.

Certified/Validated translations of the questionnaires into the corresponding languages will be used.

8.14 Physicians Assessments

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

Physician´s assessment of the extent and severity of clinical signs of psoriasis vulgaris (Redness, Thickness, Scaliness)

At SV2 and Visits 1 to 3 and early withdrawal (if applicable), the (sub) investigator will assess 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[1)], arms[2)], trunk[3)] and legs[4)] using the following scale:

0 = no involvement

1 = < 10%

2 = 10 - 29%

3 = 30 - 49%

4 = 50 - 69%

5 = 70 - 89%

6 = 90 - 100%

This assessment of extent is the percentage of that body region that is affected, and **not** the percentage BSA affected. For example, if one arm was totally affected, and the other arm was totally unaffected, the extent assessment for the arms would be 50% (half of the arms affected).

Note: [1] head includes the neck

[2] arms include hands

[3] trunk includes flexures

[4] legs include buttocks and feet

The **severity** of the psoriatic lesions in each of the four areas (head, arms, trunk, legs) 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)

Physician´s global assessment of disease severity (PGA) – body psoriasis and scalp psoriasis

At SV2 and Visits 1 to 3, and early withdrawal (if applicable), the (sub)investigator will make a global assessment of the disease severity of psoriasis of the trunk/limbs and scalp (separately) using the 5-point scale below. This assessment will represent the average lesion severity on the body and scalp, respectively. 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.

Table 13: Physician´s global assessment of disease severity (PGA)

Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red colouration but post-inflammatory hyperpigmentation may be present)
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
Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red colouration
Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red colouration
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 colouration; extreme red colouration; or deep red colouration
Note:	*PGA of the scalp should include all 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 not be included in the assessments.*

At SV2 and Visit 1 the disease severity of body psoriasis and scalp psoriasis must be graded at least as ‘mild’ in order to meet the inclusion criteria for subjects not undergoing the HPA axis testing whereas for subjects taking part in the HPA axis testing and pk sampling, the disease severity of body psoriasis and scalp psoriasis must be graded at least as ‘moderate’ at SV2 and Visit 1 in order to meet the inclusion criteria.

Physician´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 assess the extent of the subject’s total psoriatic involvement at SV2

and Visit 1. The extent of the subject's total psoriatic involvement will also be assessed at Visit 3 and early withdrawal (if applicable).

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

Physician´s Assessment of the Extent of Body Psoriasis

A baseline assessment of the extent of psoriasis vulgaris on trunk and/or limbs as percentage of the BSA 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 1% of the BSA. The extent of the subject's body psoriasis will also be assessed at Visit 3 and early withdrawal (if applicable).

Physician´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. The extent of the subject's scalp psoriasis will also be assessed at Visit 3 and early withdrawal (if applicable).

Assessment of Local Safety and Tolerability
The Assessment of Local Safety and Tolerability will be comprised of signs assessed by the (sub)investigator. The signs are not required to be reported as AEs.

At Visits 1 to 3, the (sub)investigator will assess application site reactions for the following signs: perilesional erythema, perilesional oedema, perilesional dryness, and perilesional erosion.

For perilesional erythema, oedema, dryness and erosion, the area for the (sub)investigator to assess is the perilesional area, defined as the band of skin within two (2) cm from the border of the psoriatic lesion, i.e. not the lesion itself, at any given time. The assessed signs must be present in this area, but may extend beyond it in a continuous manner.

For each sign the highest (worst) skin reaction score across all treatment areas will be recorded by use of the following 4-point scale:

Table 14: Physician's Assessment of local safety and tolerability

	0 = absent	1 = mild	2 = moderate	3 = severe
Perilesional erythema:	No perilesional erythema	Slight, barely perceptible perilesional erythema	Distinct perilesional erythema	Marked, intense perilesional erythema
Perilesional oedema:	No perilesional oedema	Slight, barely perceptible perilesional oedema	Distinct perilesional oedema	Marked, intense perilesional oedema
Perilesional dryness:	No perilesional dryness	Slight, barely perceptible perilesional dryness	Distinct perilesional dryness	Marked, intense perilesional dryness
Perilesional erosion:	No perilesional erosion	Slight, barely perceptible perilesional erosion	Distinct perilesional erosion	Marked, intense perilesional erosion

8.15 Photography

Not applicable.

8.16 Dispensing of IP

Refer to section 10.8.1.

8.17 Return of IP and Compliance

Refer to sections 10.8.1 and 10.8.3.

8.18 End of Trial Form

The End of Trial Form must be completed for all subjects who have signed informed consent. This includes e.g. date of last dose, last attended scheduled visit number, primary reason for withdrawal, etc.

9 Adverse Events

- Adverse events and serious adverse events are defined: Appendix 2 Definitions of Adverse Events and Serious Adverse Events
- Classification of adverse events in terms of serverity, causality and outcome are defined: Appendix 3 Classification of Adverse Events

9.1 Collection of Adverse Events

Adverse events must be collected from the signing of the informed consent form until the End of the trial (Visit 3, Day 28).

AEs must be assessed by medically qualified personnel.

At all visits, the subject will be asked a non-leading question by the (sub)investigator: “How have you felt since I saw you last?” No specific symptoms should be asked for. It is important that the (sub)investigator also observes the subject for any changes not reported by the subject and records these changes.

If there are no AEs to record, no further questions should be asked and “NO” should be stated in the CRF. In case there are one or more AEs to record, “YES” should be stated.

9.2 Reporting of Adverse Events in the CRF

Adverse events reported by the subject or observed by the (sub)investigator must be recorded on the adverse event form of the CRF and should be described in the following manner:

The *AE term* will be 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 AEs the *location* must be part of the AE description and may be described as either the face, scalp or trunk/limbs. Additionally, the location should 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 *duration* of the AE must be reported as the start date and stop date of the event. In addition, it must be recorded whether the AE started prior to start of trial medication.

AEs must be classified in terms of severity, causality and outcome according to the definitions in Appendix 3 Classification of Adverse Events

9.3 Actions Taken as a Consequence of an AE

Action taken with trial treatment: Any action taken with trial medication as a consequence of the AE must be recorded (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn, not applicable, unknown).

Other action taken: Any other action taken as a result of the AE must be recorded (none, concomitant medication, concurrent procedure).

Withdrawn due to AE: It must be recorded whether the AE leads to withdrawal from the trial.

9.4 Other Events to be Reported

9.4.1 Pregnancy

Any pregnancy occurring during the clinical trial must be reported to LEO within 24 hours of first knowledge using the (paper) Pregnancy Follow Up Form (Part I). All such pregnancies must be followed up until delivery or termination and final outcome must be reported on the (paper) Pregnancy Follow Up Form (Part II) within 24 hours of first knowledge.

The completed Pregnancy Follow Up Forms must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO (see section 9.5.1 for contact details).

Please also confer with section 7.8, Withdrawal Criteria.

9.4.2 Overdose

Overdose refers to the administration of a quantity of a medicinal product given per administration or per day which is above the protocol defined dosage.

The term overdose must be documented on the adverse event form of the CRF book. In addition, AEs originating from overdose must be documented on a separate line.

9.4.3 Medication Error

Medication error refers to any unintentional error in the dispensing or administration of a medicinal product while in the control of the (sub)investigator or subject. Broadly, medication errors fall into four categories: wrong medication, wrong dose (including strength, form, concentration, amount), wrong route of administration or wrong subject.

The medication error must be documented on the adverse event form of the CRF book. In addition, AEs originating from a medication error must be documented on a separate line specifying the category of error (see definitions above).

9.4.4 Misuse

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

The term misuse must be documented on the adverse event form of the CRF book. In addition AEs originating from misuse must be documented on a separate line.

9.4.5 Abuse

Abuse relates to the sporadic or persistent, intentional excessive use of an investigational product which is accompanied by harmful physical or psychological effects.

The term abuse must be documented on the adverse event form of the CRF book. In addition, AEs originating from abuse must be documented on a separate line.

9.4.6 Aggravation of Condition

Any clinically significant aggravation/exacerbation/worsening of any medical condition(s), compared to baseline, must be reported as an AE.

9.4.7 Lack of Efficacy

Not applicable.

9.5 Additional Reporting Requirements for Serious Adverse Events

9.5.1 Investigator Reporting Responsibilities

Any Serious Adverse Event (SAE) must be reported to LEO on the (paper) Serious Adverse Event Form – Clinical Trials within 24 hours of first knowledge. This report should contain an assessment of available information on seriousness, severity, causal relationship to the investigational product, comparator or trial procedure, the action taken, the outcome to date, and a narrative description of the course of the event.

The completed SAE form must be faxed or scanned and e-mailed to Global Pharmacovigilance, LEO using the following fax number or e-mail address:

Fax number: +45 7226 3287 (for Global Pharmacovigilance)
E-mail address: drug.safety@leo-pharma.com (for Global Pharmacovigilance).

It may be relevant for the (sub)investigator to enclose other information with the SAE form, such as reports of diagnostic procedures, hospital records, autopsy reports, etc.

Additionally, Global Pharmacovigilance, LEO may request further information in order to fully assess the SAE. The (sub)investigator must forward such information to Global Pharmacovigilance, LEO upon request by fax or e-mail (see contact details above).

The investigator must notify the local IRB(s)/IEC(s) of SAEs as required by current applicable legislation for the concerned country.

SAEs occurring after the completion of the clinical trial including any protocol required post-treatment follow-up period should not be routinely sought or collected. However, such events should be reported to Global Pharmacovigilance, LEO (drug.safety@leo-pharma.com) if the (sub)investigator becomes aware of them.

The criteria qualifying the AE to be an SAE should be recorded in the CRF (see section 26.2, Appendix 2).

9.5.2 LEO Reporting Responsibilities

Global Pharmacovigilance, LEO is responsible for assessing whether or not an SAE is expected. The relevant reference documents for this clinical trial are:

For the investigational product, the Investigator's Brochure, edition 5 and subsequent updates must be used (14).

For CORTROSYN® (used in the US), the latest version of the US Prescribing Information (USPI) must be used .

For Synacthen® (used in Europe) the subsequent updated SmPC for Synacthen® must be used.

Global Pharmacovigilance, LEO will notify the regulatory authorities and concerned investigators of SAEs according to the current applicable legislation for the concerned countries.

The IRB(s)/IEC(s) will be notified of SAEs according to the current applicable legislation for the concerned countries.

All SAEs that are assessed as causally related to the investigational product(s) by either the investigator or LEO, and which are not expected (Suspected, Unexpected Serious Adverse Reactions (SUSARs)) are subject to expedited reporting to regulatory authorities and IRB(s)/IEC(s) according to the current applicable legislation in the concerned countries. Investigators will be notified of these on an ongoing basis.

9.6 Follow-up for Final Outcome of Adverse Events

During the trial, the investigator should follow up for final outcome on all AEs (including SAEs). Once a subject leaves the clinical trial, the investigator should follow up on the outcome of all non-serious AEs classified as of possible/probable relationship to the investigational product for 14 ± 2 days or until the final outcome is determined, whichever comes first. SAEs must be followed up until a final outcome has been established, i.e. the follow-up may continue beyond the end of the clinical trial.

10 Investigational Product(s)

10.1 Investigational Product Description

Table 15: LEO 90100

Finished product (brand) name (if available)/name Investigational Product	LEO 90100
Formulation	Aerosol, foam
Active ingredient name/concentration	Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)
Development Number	CCI [redacted]
Excipients [not quantitative]	White soft paraffin Liquid paraffin Polyoxypropylene-11 stearyl ether all-rac-alpha-tocopherol Dimethyl ether Butane Butylhydroxytoluene (E321) (CCI [redacted])
Pack size(s)	60 g (net weight excluding propellants)
Manufacturer of bulk IP (ointment intermediate)	LEO Laboratories Ltd., 285 Cashel Road, Dublin 12, Ireland
Manufacturer of IP in primary packaging	Colep Laupheim GmbH & Co. KG Fockestrasse 12 88471 Laupheim Germany
Release testing of IP in primary packaging	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark
Manufacturer of secondary packaging and labelling	CCI [redacted]
Certifier of secondary packaging and labelling	CCI [redacted]

10.2 Administration of Investigational Products

Table 16: Administration of IP

Route of administration	Topical
Dosing frequency	Once daily
Time of day for dosing	No specific requirements
Relation of time of dosing to dietary intake	No specific requirements
Relation of time of dosing to clinical assessments	No dosing within 24 hours of Day 14 (Visit 2) and Day 28 (Visit 3) Investigational product will be applied at Visit 2 and Visit 3 under supervision of site staff after all clinical assessment have been conducted

The investigational product (IP) must be dispensed by the (sub)investigator/investigational staff at Visit(s) 1 and 2. The subject and/or parents/legal guardian should be instructed to return all dispensed investigational product (used and unused cans) at the following visit.

At Visit 1 the subject and/or parents/legal guardian will be carefully instructed (verbally and in writing by handing over a subject treatment instruction sheet) on how to apply the IP at home. The first application of the IP should be made by the subject and/or parents/legal guardian itself under supervision of the site staff. At the days of trial visits (Visit 2 and Visit 3) however, the application of IP will be done on site under supervision of site staff.

The medication should be sprayed directly on the skin at a distance of 3 to 10 cm. The foam should be gently spread with the fingertips until the medication is absorbed. The aerosol foam should be shaken before use and can be sprayed holding the can in any orientation except horizontally.

The (sub)investigator will have the discretion to determine the number of cans required to be dispensed at each dispensing visit (Visits 1 and 2).

As a guidance for the (sub)investigator the maximum weekly dose will be determined by the age and BSA at Visit 1:

- For subjects aged 12 to < 15 years with a BSA ≤ 1.3 m2, 2 cans should be dispensed for the treatment period of 14 days.
- For subjects aged 12 to < 15 years with a BSA > 1.3 m2 and subjects aged > 15 years with a BSA ≤ 1.7 m2, 3 cans should be dispensed for the treatment period of 14 days.
- For subjects aged > 15 years with a BSA > 1.7 m^2, 4 cans should be dispensed for the treatment period of 14 days.

The BSA will be calculated using the Mosteller formula (Appendix 9).

Subjects taking part in the HPA axis / Pk assessments:

For subjects performing HPA axis and PK assessments, being treated under maximal use conditions, a maximum weekly dose will not be established. The (sub)investigator is to ensure the subject has enough investigational product to apply to all affected areas of the body and scalp once daily.

10.3 Precautions/Overdosage

Overdose with calcipotriol may be associated with hypercalcaemia. Clinically important hypercalcaemia will be managed at the investigator's discretion with rehydration, bisphosphonate administration or according to local standard of care. Hypercalcaemia should rapidly subside when treatment is discontinued.

Overdose with corticosteroid containing products may result in suppression of adrenal function which is usually reversible. In such cases, symptomatic treatment is indicated. In case of chronic toxicity, corticosteroid treatment must be discontinued gradually.

10.4 Packaging of Investigational Products

Individual Visit Kits

Individual cans containing LEO 90100 will be dispensed at each visit by the site. The number of cans dispensed at each visit is dependent on the subject's age and BSA at Visit 1. Each single can will be labelled with a unique kit number and packed in a covering carton.

Immediate Treatment Packaging - Individual Unit (Cans)

The primary packaging for LEO 90100 aerosol foam consists of an aluminium can into which the formulation is pre-filled and subsequently administered through a continuous valve.

Each individual unit contains 60 g of Investigational Product.

The labelling of trial products must be in accordance with Europen Union (EU) Annex 13, local regulations and trial requirements.

10.5 Storage of Investigational Products

All LEO supplied drugs must be stored in a secure and restricted area under the conditions specified on the label and remain in the original container until dispensed.

Furthermore, the following storage conditions and handling precautions should be observed:

LEO 90100 aerosol foam:

- Shake before use
- Wash hands before and after use
- Keep away from heats/sparks/open flames/hot surfaces/sunlight
- Keep out of the reach of children
- Do not inhale
- Do not smoke
- Do not exceed temperatures above 50°C (122°F)
- Do not pierce or burn, even after use
- EU storage conditions: Store at 2°C (35.6°F) to 25°C (77°F). Do not freeze
- US storage conditions: Store at 20°C (68°F) to 25°C (77°F). Excursions between 15°C to 30°C permitted. Do not freeze

10.6 Treatment Assignment

Subjects who have been found to comply with all the protocol's inclusion and exclusion criteria will start treatment and be dispensed with investigational product at Visit 1. Each can will have a unique kit number. When a can is dispensed to the subject, the unique kit number for that can will be recorded in the subject's medical record and the CRF.

10.6.1 Randomisation Code List

Not applicable.

10.7 Non-Investigational Medicinal Products

10.7.1 CORTROSYN® (cosyntropin)/Synacthen® for injection

CORTROSYN® (used in the US) 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).

Synacthen® (used in Europe) is a commercial solution for injection containing tetracosactidhexaacetate that will be used for the ACTH challenge test. One ampoule contains 1 ml of 0.28 mg tetracosactid-hexaacetate (0.25 mg tetracosactid which equals 25 IU ACTH).

CORTROSYN®/Synacthen®will be sourced by the investigational sites.

CORTROSYN® will be used in accordance with the USPI for the marketed product .
Synacthen® will be used in accordance with the subsequent updated SmPC.

Table 17: CORTROSYN® (used in the US)

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	Amphastar Pharmaceuticals, Inc. Rancho Cucamonga, CA 91730 U.S.A.
Supplier's name	Not Applicable.
Certifier's name	Amphastar Pharmaceuticals, Inc. Rancho Cucamonga, CA 91730 U.S.A.

Table 18: Synacthen® (used in Europe)

Finished product (brand) name (if available)/name investigational product	Synacthen®
Formulation	Solution for injection
Active ingredient name/concentration	Tetracosactid 0.25 mg/mL (i.e., 25 IU ACTH)
Excipients	Acetic acid, sodium acetate, sodium chloride, aqua ad inject.
Pack size(s)	Ampoules: 10 times 1 ml
Manufacturer's name	Products available on the local market will be used (according to the local marketing authorisation) To be sourced individually by sites (excluding Poland and Romania)
Supplier's name	See above
Certifier's name	See above

10.7.1.1 Packaging and Labelling

The marketed product, as available in the US or in Europe will be used for this study without any re-labelling or re-packaging of the product. US and the Netherlands will be responsible for purchasing the CORTROSYN®/Synacthen® , they will be reimbursed for the non-investigational IP. Poland and Romania will be provided the Synacthen® through the depot Catalent in Bathgate, UK.

10.7.1.2 Storage of Non-Investigational Medicinal Products

CORTROSYN®/Synacthen® should be stored in a safe and secure place inaccessible for children. The temperature for storage should be 15 to 30°C for CORTROSYN®. Synacthen® should be protected from light and stored in a refrigerator (2 - 8°C). The Investigator is responsible for ensuring that the storage of CORTROSYN®/Synacthen®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

For CORTROSYN®/Synacthen® 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®/Synacthen®should be used promptly and should not be retained. Any unused portion should be discarded.

10.7.1.4 Precautions

Prior to injection of CORTROSYN®/Synacthen®, the investigator and staff must be prepared to treat any possible anaphylactic/allergic/hypersensitivity reaction. Severe anaphylactic reactions to CORTROSYN®/Synacthen®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®/Synacthen® 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 USPI for CORTROSYN® and the SmPC for Synacthen® for further details).

10.7.2 0.9% Sodium Chloride Injection, USP

0.9% Sodium Chloride Injection, USP will be sourced by the investigational sites in the US and Europe 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 US and Europe 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.

10.8 Drug Accountability and Compliance Checks

10.8.1 Drug Accountability

10.8.1.1 Drug Accountability Investigational Product

The investigator is fully responsible for the investigational products at the trial site, for maintaining adequate control of the investigational products, and for documenting all transactions with them.

Dispensing of investigational products may be delegated, e.g. to a hospital pharmacy, as locally applicable.

At each visit, the investigational product, including (empty) cans dispensed at the previous visit, must be returned by the subject. An inventory (Individual Drug Accountability Form) must be kept, tracking the 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 the investigational product.

All investigational products supplied by the Contract Manufacturing Organisation (CMO) on behalf of LEO must be returned to the CMO. Prior to their return, they must be fully accounted for by the monitor with the help of the person responsible for dispensing the investigational products. Accountability must be documented by using 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 running the clinical trial.

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

10.8.1.2 Drug Accountability Non-Investigational Medicinal Products

The investigator is fully responsible for the non-investigational medicinal products (i.e. CORTROSYN®/Synacthen®and 0.9% Sodium Chloride Injection) at the trial site. Dispensing of non-investigational medicinal products may be delegated, e.g. to a hospital pharmacy, as locally applicable.

The person responsible for dispensing the non-investigational medicinal products will be responsible for maintaining adequate control and for documenting all transactions. All non-investigational medicinal products 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 non-investigational medicinal products dispensed for each subject in the trial. The batch number/lot number and expiry date of the non-investigational medicinal products dispensed will be recorded. This inventory must be available for inspection at monitoring visits and will be checked to ensure correct dispensing of non-investigational medicinal products.

10.8.2 Trial Product Destruction

Used and unused trial products will be destroyed by the CMO according to LEO procedures.

10.8.3 Treatment Compliance

At all on-treatment visits, the subject should be asked if she/he has used the investigational product as prescribed. If a subject is found to be non-compliant, the (sub)investigator should remind the subject of the importance of following the instructions given including taking the trial products as prescribed. The degree of non-compliance and the reason for it must be recorded in the CRF.

10.9 Emergency Unblinding of Individual Subject Treatment

Not applicable.

11 Statistical Methods

11.1 Determination of Sample Size

The primary objective of the trial is to evaluate the safety of LEO 90100. No formal sample size calculation evaluating the power of the trial has been performed. However, a consideration regarding the sample size was made as described below.

For adverse events with a true (theoretical) frequency of at least 2% the probability of observing at least one case among the 100 subjects will be at least 86.7%.

11.2 Definition of Trial Analysis Sets

All subjects enrolled in the trial (i.e. subjects for whom informed consent has been obtained and who have been registered in a clinical trial) will be accounted for in the clinical trial report.

All subjects assigned treatment are included in the full analysis set and will be analysed for efficacy. Exclusions from the full analysis set can be considered in special cases as described in ICH E9, section 5.2.1., Full Analysis Set. If it is decided to exclude a subject assigned treatment from the full analysis set, a justification addressing ICH E9 will be given.

For the analysis of the results from the ACTH-challenge test, a per protocol analysis set will be defined by including subjects undergoing HPA axis assessments from the full analysis set, however excluding the subjects who:

- receive no treatment with the investigational product
- provide no results for the ACTH-challenge test at Week 4
- and/or do not fulfil the inclusion criterion concerning evidence of adrenal function at baseline (i.e. inclusion criterion 17).

A safety analysis set will be defined by excluding subjects from the full analysis set who either received no treatment with investigational product and/or for whom no post-baseline safety evaluations are available.

For the analysis of PK data, a PK analysis set will be defined by including subjects undergoing PK assessments from the full analysis set, however excluding the subjects who:

- receive no treatment with the investigational product.
- provide no PK data at Week 4.

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

11.3 Statistical Analysis

11.3.1 Disposition of Subjects

The reasons for leaving the trial will be presented for all subjects assigned treatment by last visit attended.

11.3.2 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects assigned treatment and separately for per protocol analysis set. Presentations of age, sex, ethnicity, race and baseline disease severity according to the PGA on the body and scalp will also be given by centre.

Demographics include age, sex, race, ethnicity and skin type. Other baseline characteristics include height, weight and BMI, duration of plaque psoriasis, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, PGA on the body and scalp, PASI (calculated from the physician's assessment of extent and severity of the clinical signs), physician's assessment of extent of psoriasis vulgaris (total involvement as % of BSA, on trunk and/or limbs as % of BSA and on scalp as % of scalp area) and subject´s global assessment of disease severity on the body and scalp.

11.3.3 Exposure and Treatment Compliance

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

The amount of IP used (g) and the average weekly amount of IP used (g) will be summarised for safety analysis set and also for per protocol analysis set and separately for three different treatment periods (the first two weeks, the second two weeks and the total treatment period). Furthermore, a plot of the average weekly amount of IP use over the total treatment period against baseline extent of total BSA involvement will be presented for both analysis sets.

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

11.3.4 Analysis of Primary Endpoints

Adverse events

The number and percentage of subjects experiencing each type of adverse event will be tabulated for the safety analysis set. Further details are included in section 11.3.8.1.

Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4

The analysis of the results from the ACTH-challenge test will be based on the per protocol analysis set.

The number and percentage of subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 will be tabulated.

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

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 and FU2, respectively, will be listed for each subject with a value ≤18 mcg/dl at either 30 or 60 minutes after ACTH-challenge. Values ≤ 18 mcg/dl at 30 or 60 minutes after ACTH-challenge will be flagged.

Change in albumin-corrected serum calcium from baseline (SV2) to Week 4

The analysis of the albumin-corrected serum calcium data will be based on the safety analysis set.

For the albumin-corrected serum calcium, the absolute value by visit and at end of treatment and the change from baseline (SV2) to Week 4 and to end of treatment will be summarised. Furthermore, the 95% confidence interval (CI) of mean change from baseline to Week 4 and to end of treatment will be presented. In addition, the albumin-corrected serum calcium will be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value is below, within or above the reference range, respectively. Shift table will be produced showing the categories at baseline (SV2) against those at Week 4 and at end of treatment.

Summary tables and shift table will be repeated subgrouped by baseline 25-hydroxy vitamin D classifications (‘low’, ‘normal’ or ‘high’ with respect to its reference range).

Plots of the average weekly amount of IP use over the total treatment period against change from baseline to Week 4 and against change from baseline to end of treatment in albumin-corrected serum calcium will be presented.

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

Change in calcium excretion from baseline (SV2) to Week 4 in 24-hour urine

The analysis of the 24-hour urinary calcium excretion data will be based on a subset of the safety analysis set including the subjects undergoing HPA axis testing. The analysis will be performed as outlined above for the analysis of the albumin-corrected serum calcium data.

In addition, calcium excretion at the 24-hour urine collection will also be presented separately for 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 (29).

Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in 24-hour urine

The analysis of the 24-hour urinary calcium:creatinine ratio data will be based on a subset of the safety analysis set including the subjects undergoing HPA axis testing. The analysis will be performed as outlined above for the analysis of the albumin-corrected serum calcium data.

11.3.5 Analysis of Secondary Endpoints

Subjects with serum cortisol concentration ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4

Subjects with a serum cortisol concentration ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4 will be analysed as described for subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 in section 11.3.4.

Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in spot urine

The analysis of the calcium:creatinine ratio in spot urine will be based on a subset of the safety analysis set including the subjects not undergoing HPA axis testing. The analysis will be performed as described for the analysis of the albumin-corrected serum calcium data in section 11.3.4.

Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician's global assessment of disease severity on the body at Week 4

The statistical analysis of efficacy will be based on the full analysis set. The percentage of subjects who achieve 'treatment success' according to the PGA on the body will be presented by visit and at end of treatment. The 95% CI, which is based on a binomial distribution, will be presented for the proportion of subjects with 'treatment success' at Week 4 and at end of treatment.

The percentage of subjects who achieve 'treatment success' according to the PGA on the body at Week 4 and at end of treatment will also be tabulated by age-group, sex, ethnicity, race, centre and baseline PGA on the body.

Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician's global assessment of disease severity on the scalp at Week 4

Subjects with 'treatment success' according to the PGA on the scalp will be analysed as outlined above for the body.

Percentage change in PASI from baseline (V1) to Week 4

PASI is calculated using the formula given below based on the physician's assessment of the extent and severity of the disease locally (head, trunk, arms, legs) (8.14).

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.

The percentage change in PASI from baseline (V1) to each visit and to end of treatment will be summarised for the full analysis set. The 95% CI for mean percentage change in PASI based on a normal distribution will be calculated for Week 4 and for end of treatment.

Subjects with 'treatment success' (i.e., 'clear' or 'very mild) according to the subject's global assessment of disease severity on the body at Week 4

The percentage of subjects who achieve 'treatment success' according to the subject's global assessment of disease severity on the body will be presented by visit and at end of treatment for the full analysis set. The 95% CI based on a binomial distribution will be calculated for the proportion of subjects with 'treatment success' at Week 4 and at end of treatment.

Subjects with 'treatment success' (i.e., 'clear' or 'very mild) according to the subject's global assessment of disease severity on the scalp at Week 4

Subjects with 'treatment success' according to the subject's global assessment of disease severity on the scalp will be analysed as outlined above for the body.

Change in itch as assessed by the VAS from baseline (V1) to Week 4

The change in itch as assessed by the VAS from baseline (V1) to each visit and to end of treatment will be summarised for the full analysis set. The 95% CI for mean change in itch based on a normal distribution will be calculated for Week 4 and for end of treatment.

11.3.6 Exploratory Analysis of Efficacy

The exploratory analysis of efficacy will be based on the full analysis set.

The PGA on the body and on the scalp, PASI and subject's global assessment of disease severity on the body and on the scalp will be summarised by visit and at end of treatment.

The physician's assessment of extent of psoriasis (total involvement as % of BSA , on trunks and/or limbs as % of BSA and on scalp as % of scalp area) will be summarised by visit and at end of treatment.

11.3.7 Analysis of Patient-Reported Outcomes

Subject's assessment of itch

Subject's assessment of itch will be summarised by visit and at end of treatment for the full analysis set.

Subject's assessment of itch-related sleep loss

Subject's assessment of itch-related sleep loss will be summarised by visit and at end of treatment for the full analysis set. In addition, the change from baseline to each visit and to end of treatment will be summarised.

Children's Dermatology Life Quality Index

The CDLQI total score will be analysed as outlined above for subject's assessment of itch-related sleep loss.

Additionally, the percentage of subjects with CDLQI scores of 0 or 1 indicating no or minimal impact on quality of life will be presented by visit and at end of treatment including only the subjects with the baseline score of > 1.

Furthermore, the percentage of subjects with ≥ 5 points improvement in CDLQI score from baseline will be presented by visit and at end of treatment for the subjects with the baseline score ≥ 5.

The Family Dermatology Life Quality Index

The FDLQI total score will be analysed as outlined above for the CDLQI.

11.3.8 Analysis of Safety

The analysis of safety will be based on the safety analysis set, except where otherwise stated.

11.3.8.1 Adverse Events

Adverse events will be coded during the course of the trial according to MedDRA. Adverse events will be presented by preferred terms and primary system organ class.

Treatment emergent AEs will be summarised, however 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 started after the first application of investigational product or if started before the first application of investigational product (applicable if subject had a

wash-out) and worsened in severity thereafter. The tabulations described in the following will only include the events that are emergent with trial treatment. In each of the tabulations, adverse events are defined by MedDRA preferred terms within primary system organ class.

An overall summary of the number (percentage) of subjects with any treatment emergent AEs, SAEs, premature discontinuations from the trial due to AEs, treatment related AEs and severe AEs will be presented.

The number of subjects experiencing each type of adverse events will be tabulated regardless of the number of times each adverse event is reported by each subject.

The severity for each type of adverse event will be tabulated. Where there are several recordings of severity for a given type of adverse event, severity will be taken as the most severe recording for that adverse event.

The causal relationship to trial medication for each type of adverse events will be tabulated. Where there are several recordings of causal relationship to the investigational product 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 (sub)investigator will be in possession of most information and so best able to judge causal relationship.

Related adverse events are defined as adverse events for which the (sub)investigator has not described the causal relationship to investigational product as ‘not related’. The number of subjects experiencing each type of related adverse event will be tabulated regardless of the number of times each related adverse event is reported by each subject.

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 will be tabulated.

Serious adverse events will be evaluated separately and a narrative for each will be given.

AEs leading to withdrawal from trial or discontinuation of investigational product will be listed.

11.3.8.2 Vital Signs

For vital signs (systolic and diastolic blood pressure, heart rate and temperature), the absolute value by visit and change from baseline (SV2) to each visit will be summarised.

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

11.3.8.3 Local Safety and Tolerability

For each of the assessments of local safety and tolerability, the number and percentage of subjects in each of the four categories ('Absent' to 'Severe') will be tabulated at each visit.

11.3.8.4 Clinical Laboratory Evaluation

The albumin-corrected serum calcium, 24-hour urinary calcium excretion and 24-hour urinary calcium:creatinine ratio will be analysed as outlined in section 11.3.4. The calcium:creatinine ratio in spot urine will be analysed as described in section 11.3.5.

For other biochemistry and haematology parameters, the absolute value by visit and the change from baseline (SV2) to Week 4 will be summarised. In addition, the laboratory parameters will be classified as 'low', 'normal' or 'high', depending on whether the value is below, within or above the reference range, respectively. Shift tables will be produced showing the categories at baseline (SV2) against those at Week 4. However, as 25-hydroxy vitamin D will be assessed only at baseline (SV2) then only the baseline values will be summarised.

The 24-hour urinalysis parameters not described in section 11.3.4 will be analysed for a subset of the safety analysis set including the subjects undergoing HPA axis testing as outlined above for the biochemistry and haematology parameters.

Urinalysis parameters measured in spot urine and not described in section 11.3.5 will be analysed for a subset of the safety analysis set including the subjects not undergoing HPA axis testing. The analysis will be performed as outlined above for the biochemistry and haematology parameters.

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.

11.3.8.5 PK evaluation

The PK analysis will be based on the PK analysis set. The following PK parameters will be calculated at Week 4, if possible, for each assayed compound based on the obtained plasma concentrations: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max} and $T_{1/2}$.

If it is not possible to calculate the above PK parameters at Week 4, samples with plasma concentration above lower limit of quantification (LLOQ) will be presented.

For Week 2, the plasma concentrations above the lower limit of quantification will be presented as only one pre-dose trough sample will be collected at Week 2.

11.3.9 Interim Analysis

No interim analyses are planned.

11.3.10 General Principles

All confidence intervals will be presented with 95% degree of confidence.

An observed cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit).

The end of treatment values will be presented for laboratory parameters (primary and secondary endpoints), for efficacy data and for patient-reported outcomes data. Definition of the end of treatment value is given below in section 11.3.11.

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

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

Any changes from the statistical analysis planned in this clinical trial protocol will be described and justified in a protocol amendment and/or in the clinical trial report dependent on the type of deviation.

11.3.11 Handling of Missing Values

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 3 (Week 4). However, for laboratory parameters this will be the last value recorded after baseline (SV2) up to and including Visit 3.

12 Trial Committees

Not applicable.

13 Case Report Forms and Data Handling

13.1 Case Report Forms (CRFs)

Data will be collected by means of Electronic Data Capture (EDC). The investigator or staff authorised by the investigator must enter subject data into electronic CRFs. Data recorded in the electronic CRFs must 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.

The investigator must electronically sign all CRFs used. This signature information (including date of signature) will be kept in the audit trail and cannot be altered. Any correction(s) made by the investigator or authorised site staff to the CRF after original entry will be documented in the audit trail. Previously approved changes to the data, will require the re-signature of the investigator. The person making the change and the date, time and reason for the change will be identified in the audit trail.

For archiving purposes, each investigator must 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 and before access to the eCRF is revoked. Audit trail information must be included. CRFs must be available for inspection by authorised representatives from LEO (e.g. audit by the quality assurance department), from regulatory authorities and/or IEC/IRBs.

13.2 Data Handling

Subject data should be entered into the eCRF as soon as possible after the visit in accordance with the time requirements described in the Clinical Trial Agreement with the site. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the trial 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.

13.3 Source Data

For all data recorded, the source document must be defined in a source document agreement at each trial site. There must only be one source defined at any time for any data elements.

The trial monitor will check the CRFs for accuracy and completeness by verifying data recorded in the CRF against source data to ensure such records are consistent.

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 not normally collected as a

routine part of the clinical practice at the site may be entered on a worksheet. Clinical assessments/safety evaluations must be signed by medically qualified (sub)investigators.

If the worksheet does not become part of the subject's medical record, 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, including plaque psoriasis and other skin diseases
- 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
- Lot number/batch number of non-investigational medicinal products used for each subject
- Concomitant medication (including changes) and diagnoses
- Subject demographics (sex, date of birth, race, ethinic origin, Fitzpatrick skin type)
- Clinical assessments (vital signs, physical examination, investigator's assessments: PGA, extent of psoriasis, monitoring of local tolerability and safety)
- Laboratory assessments (time of start and stop for CORTOSYN®/Synacthen® injections and time of sampling for cortisol, PK, haematology, biochemistry and urine tests)
- Time of application, start and stop for subjects taking part in the HPA axis testing and PK sampling on SV2, Visit 2 and Visit 3
- 24-hour urine collection (start and stop times, incomplete collection, spillage and storage temperature excursions) for subjects taking part in the HPA axis testing and PK sampling
- Adverse events, (nature, dates)
- Dietary calcium intake diary

In addition to the above, the following should be added to the subject's medical record in chronological order:

- Date(s) of conducting the informed consent process including date of provision of subject information
- CRF book number/Subject number
- Investigational product kit number
- The fact that the subject is participating in a clinical trial in plaque psoriasis for 4 weeks
- Other relevant medical information

13.4 Trial Monitoring

During the course of the trial, the monitor will visit the trial site to ensure that the protocol and GCP are adhered to, that all issues have been recorded to perform source data verification and to monitor drug accountability

The first monitoring visit should be performed as soon as possible after FSFV and no later than 10 days after.

The monitoring visit intervals will depend on the trial site's recruitment rate, the compliance of the trial site with the protocol and GCP.

In order to perform their role effectively, monitors and persons involved in quality assurance and inspections will need direct access to source data, e.g. medical records, laboratory reports, appointment books, etc. If the electronic medical record does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

14 Handling of an Urgent Safety Measure

An Urgent Safety Measure is a measure taken to implement an action/protocol deviation under an emergency. This is defined within the EU Directive as *"…the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard.*" (Article 10(b) of Directive 2001/20/EC).

If the investigator becomes aware of information that necessitates an immediate change in the clinical trial procedure or a temporary halt to the clinical trial in order to protect clinical trial subjects from any immediate hazard to their health and safety, the investigator can do so without prior approval from LEO, regulatory authority(ies) or IRB(s)/IEC(s).

The investigator must immediately inform LEO - by contacting the ICTM or medical expert - of this change in the clinical trial procedure or of the temporary halt providing full details of the information and the decision making process leading to the implementation of the urgent safety measure.

LEO must act immediately upon receipt of the urgent safety measure notification in accordance with the internal procedures.

15 Quality Assurance/Audit

The clinical trial will be subject to audits conducted by LEO or inspections from domestic or foreign regulatory authorities or from IRBs/IECs. Audits and inspections may take place during or after the trial. The investigator and the site staff as well as LEO staff have an obligation to cooperate and assist in audits and inspections. This includes giving auditors and inspectors direct access to all source documents and other documents at the trial site relevant to the clinical trial. This includes permission to examine, verify and reproduce any records and reports that are important to the evaluation of the trial.

If the trial site is contacted for an inspection by competent authorities, LEO must be notified immediately.

16 Completion of Trial

16.1 Trial Completion Procedures

End of trial is defined as 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 must undertake arrangements for the collection and disposal of any unused trial material that the investigator is not required to keep in his/her files.

16.1.1 Criteria for Premature Termination of the Trial and/or Trial Site

LEO, the investigator, the IRB/IECs or competent authorities may decide to stop the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained.

If a trial is suspended or prematurely terminated, the investigator must inform the subjects promptly and ensure appropriate therapy and follow-up. As specified by applicable regulatory requirements, either the investigator or LEO must promptly inform IRB/IECs and provide a detailed written explanation. Relevant competent authorities must be informed.

The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavourable for the continuation of the trial.

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.

16.3 Archiving of Trial Documents

The investigator at each trial site must make arrangements to store essential trial docu-ments, including the Investigator Trial File (ICH E6, Guideline for Good Clinical Practice) until LEO informs the investigator that the documents are no longer to be retained or longer if required by local regulations.

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 the completion of the trial (e.g. in case of an inspection from regulatory authorities).

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

The destruction process must ensure confidentiality of data and must be done in accordance with local regulatory requirements.

17 Ethics and Regulatory Authorities

17.1 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Regulatory Authorities

Written approval or favourable opinion must be obtained from relevant IRB/IECs prior to the enrolment of subjects.

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

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

17.2 Ethical Conduct of the Trial

This clinical trial must be conducted in accordance with the principles of the current revision at the start of the trial of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

17.3 Subject Information and Informed Consent

The subject's signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations.

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).

The subject's signed and dated informed consent to participate in the clinical trial must be obtained prior to any clinical trial related procedure being carried out in accordance with ICH GCP (4.8) and all applicable laws and regulations.

17.4 Processing of Personal Data

This protocol specifies the personal data on trial subjects (e.g. age, gender, health condition, height, medical history, test results, etc.) which shall be collected as part of the trial and processed during and after trial completion.

Personal data collected as part of the clinical trial will be transferred to/from the institution/investigator and LEO.

Processing of personal data on behalf of LEO requires a written agreement between LEO and the relevant party which covers collection, processing and transfer of personal data in the clinical trial. In certain cases, an agreement on transfer of personal data may also be required.

Investigators and LEO must ensure that collection, processing and transfer of personal data are in compliance with national legislation on data protection and privacy.

The investigator/institution may be considered as data controllers when they wish to use personal data collected in the clinical trial for their own purpose such as publication of clinical trial results.

Subjects (or their legally acceptable representative) must be asked to consent to the collection, processing and transfer of their personal data to EU and non-EU countries for the purpose of conducting the clinical trial, research and development of new or existing products/services, improving existing products/services, applying for marketing authorisations for products/services, marketing of products/services and other related activities.

If required, LEO will obtain the necessary authorization(s) for processing by LEO of personal data collected in the trial.

18 Insurance

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

19 Use of Information

This clinical trial 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 belonging to LEO and shall not be used by the investigator for purposes other than this clinical trial.

The investigator agrees that LEO 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.

20 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 (30) (31).

Results will be made available on LEO's web site according to LEO's position on access to clinical trial information.

This clinical trial is multi-centre, 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 and the members of a writing committee, which shall be appointed by LEO.

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 have been received, defined as database 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 a copy of all such manuscripts, and LEO shall have rights to review and comment. Upon the request of LEO, 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, delay the publication or presentation to allow LEO to protect its inventions and other intellectual property rights described in any such manuscripts. In case the first multi-centre publication is still ongoing and has not been made public at the time of notification, LEO 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 also subscribes to the joint position of the innovative pharmaceutical industry (32) for public disclosure of clinical trial results in a free, publicly accessible database, regardless of outcome.

21 Responsibilities

The international coordinating investigator (ICI) is responsible for the approval of the (Consolidated) Clinical Trial Protocol, Clinical Trial Protocol Amendment(s) and the Clinical Trial Report on behalf of all clinical trial investigators and as agreed to in an international coordinating investigator agreement.

The national coordinating investigator(s) are responsible for national issues relating to the clinical trial as agreed to in a national coordinating investigator agreement.

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.

22 List of Abbreviations

ACTH	Adrenocorticotrophic Hormone
AE	Adverse Event
ALP	Alkaline Phosphatase
AUC	Area Under Curve
BDP	Betamethasone Dipropionate
BSA	Body Surface Area
°C	Celsius
CDLQI	Children´s Dermatology Life Quality Index
CDMS	Clinical Data Management System
CEE	Central and Eastern Europe
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CMO	Contract Manufacturing Organisation
CRF	Case Report Form
CRO	Contract Research Organisation
DME	Dimethyl Ether
EDC	Electronic Data Capture
EU	European Union
F	Fahrenheit
FDA	Food and Drug Administration
FDLQI	Family Dermatology Life Quality Index
FSFV	First Subject First Visit
FU	Follow-Up
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HPA	Hypothalmic-Pituitary-Adrenal
Hrs	Hours
IB	Investigator´s Brochure
ICH	International Conference on Harmonisation
ICI	International Coordinating Investigator

ICTM	International Clinical Trial Manager
ID	Identification
IND	Investigational New Drug
IP	Investigational Product
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International Unite
LSLV	Last Subject Last Visit
LLOQ	Lower Limit of Quantification
mcg	microgram
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	miligram
ml	mililiter
mmHg	millimetre(s) of mercury
MUSE	Maximal Use Systemic Exposure
PASI	Psoriasis Area and Severity Index
PTH	Parathyroid Hormone
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PK	Pharmacokinetic
PUVA	Psoralen plus Ultraviolet light A
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SV	Screening Visit
$T_{½}$	Elimination half life
T_{max}	Time of Maximum plasma concentration

TBD	To be determined
US	United States
USP	United States Pharmacopeial Convention
USPI	US Prescribing Information
UVB	Ultraviolet light B
V	Visite
VAS	Visual Analogue Scale
WBC	White Blood Cell
WMA	World Medical Association

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24 List of Appendices

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Appendix 9: Mosteller Formular

25 Appendix 1: Protocol Summary

Name of finished/ investigational product	LEO 90100 aerosol foam
Name of active substance	Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)
Title of trial/trial ID/EudraCT no.	Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to < 17 Years) with Plaque Psoriasis/LP0053-1108/2015-000839-33
Coordinating investigator(s)	International coordinating investigator: Marieke Seyger, MD, PhD (the Netherlands)
Sponsor's name/ address	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark
Estimated number of trial sites and distribution	The trial is planned to be conducted in North America, Central and Eastern Europe. Approx. 30 sites across North America and CEE.
Trial period	Planned FSFV: Q3 2015 Planned Last Subject Last Visit (LSLV): Jan 2017
Main objective(s)	The primary objective is to evaluate the safety of once daily use of LEO 90100 in adolescent subjects (aged 12 to < 17 years) with plaque psoriasis on the body and scalp.
Methodology	The present trial is designed as an international, multi-centre, prospective, open-label, non-controlled, single-group, 4-week trial in adolescent subjects (aged 12 to < 17 years) with plaque psoriasis.
Number of subjects to be enrolled	In total, a sufficient number of subjects will be enrolled to ensure 100 subjects are available for evaluation of the effect of LEO 90100 on the calcium metabolism. The 100 subjects include the enrolment of 30 evaluable subjects without adrenal suppression at baseline who undergo an ACTH-challenge test (Visit 3) and PK assessments (Visit 2 and Visit 3). The ACTH-challenge test as well as PK assessments will only be performed at assigned sites and countries.
Main criteria for inclusion (all subjects)	• Adolescent subjects (age 12 to 16 years, 11 months). • Plaque psoriasis on trunk and/or limbs affecting at least 2% BSA. • Plaque psoriasis on the scalp affecting at least 10% of total scalp area. • A total psoriatic involvement on trunk, limbs and scalp not exceeding 30% BSA. • PGA score of at least mild on trunk and/or limbs at SV1, SV2 and V1.

	• PGA score of at least mild on scalp at SV1, SV2 and V1.
	• A serum albumin-corrected calcium below the upper reference limit at SV2.
	• Female subjects must be of either
	  • non-childbearing potential, i.e. premenarchal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus or has tubal litigation) or,
	  • child-bearing potential provided there is a confirmed negative pregnancy test prior to trial treatment to rule out pregnancy.
	• Female subjects of child-bearing potential must be willing to use highly effective contraception at trial entry and until completion.

Main criteria for inclusion (for subjects undergoing HPA axis testing:)	• Plaque psoriasis on trunk and/or limbs affecting at least 10% BSA. • Plaque psoriasis on the scalp affecting at least 20% of total scalp area. • PGA score of at least moderate on trunk and limbs at SV1, SV2 and V1. • PGA score of at least moderate on scalp at SV1, SV2 and V1. • Normal HPA axis function at SV2 (serum cortisol concentration above 5 mcg/dl before ACTH challenge and serum cortisol concentration above 18 mcg/dl 30 minutes after ACTH challenge).

Main criteria for exclusion (for all subjects)	• A history of hypersensitivity to any component of LEO 90100.
	• 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 V1 and during the trial:
	  a. etanercept – within 4 weeks prior to V1
	  b. adalimumab, infliximab – within 2 months prior to V1
	  c. ustekinumab – within 4 months prior to V1
	  d. experimental products – within 4 weeks/5 half-lives (whichever is longer) prior to V1
	• Systemic treatment with therapies other than biologicals, with a possible effect on scalp and/or body psoriasis (e.g. methotrexate, retinoids, immunosuppressants) within 4 weeks prior to V1 or during the trial.
	• PUVA therapy within 4 weeks prior to V1.
	• UVB therapy within 2 weeks prior to V1 or during the trial.
	• Any topical treatment on the scalp and body including corticosteroids and vitamin D (except for emollients and non-steroid medicated shampoos) within 2 weeks prior to V1 or during the trial.
	• Systemic calcium, vitamin D supplementation > 400 IU/day, antacids, diuretics,

	antiepileptics, diphosphonates or calcitonin within 4 weeks prior to SV2 or during the trial. (note: stable dose of vitamin D supplementation ≤ 400 IU/day is permitted provided there are no dose adjustments during the study period).
Main criteria for exclusion (for subjects undergoing HPA axis testing:)	• A history of serious allergy, allergic asthma or serious allergic skin rash. • Known or suspected hypersensitivity to any component of CORTROSYN®/ Synacthen®(including ACTH/cosyntropin/tetracosactide) • Systemic treatment with corticosteroids (including inhaled and nasal steroids) within 12 weeks prior to SV2 or during the trial. • 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. • Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to SV2 or during the trial. • Systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole,metronidazole) within 4 weeks prior to SV2 or during the trial. Topical ketoconazole within 2 weeks prior to SV2.
Investigational product(s)	LEO 90100 aerosol foam, containing calcipotriol (as hydrate) 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate), 60 g per can, applied once dailyto body and scalp psoriasis lesions
Investigational reference product(s)	Not applicable.
Duration of treatment	The screening period including any washout period will last for 7-28 days, depending on the prior use of excluded treatments. The treatment period will be 4 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.

Main assessments	**Safety Assessment** Laboratory analysis: the following laboratory tests will be taken at SV2 and Visit 3 (Day 28). • haematology: hemoglobin, haematocrit, red blood cells (RBC), mean corpuscular volume (MCV), white blood cells (WBC) including differential count and platelets. • biochemistry (serum/plasma): cortisol (only for subjects in HPA Axis Cohort), urea, creatinine, albumin, sodium, potassium, chloride, calcium, phosphate, ALP and PTH. • urinalysis on 24-hour urine: calcium, phosphate, creatinine, volume. • urinalysis on spot urine: glucose, ketones, calcium, phosphate and creatinine At SV2 only, the vitamin D status will be assessed by the following laboratory analysis: • 25-hydroxy vitamin D Calcium metabolism evaluation will include serum albumin-corrected calcium, phosphate, alkaline phosphatase (ALP) and plasma parathyroid hormone (PTH) on a blood sample taken at SV2 and after 4 weeks of treatment. 24-hour urine (only for subjects undergoing HPA axis testing) and spot urine will be collected at SV2 and after 4 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/spot urine collection. Subjects will be instructed to keep a diary of daily intake of calcium-rich nutrients in these periods. ACTH challenge test: For subjects performing HPA axis assessments: the ACTH challenge test will be performed on 2 occasions: At SV2 and Visit 3 (Day 28). In addition, an ACTH challenge test will be performed at Visit FU2 for subjects with possible HPA axis suppression at Visit 3. Vital signs: Blood pressure and temperature will be measured at SV2 and Visit 3 (Day 28). Adverse events: Adverse events will be recorded at all visits after SV1 (if applicable). Assessment of Local Safety and Tolerability At all treatment phase visits, the Assessment of Local Safety and Tolerability will comprise of perilesional signs of erythema, oedema, dryness and erosion assessed by the (sub)investigator. For each sign the highest (worst) skin reaction score across all treatment areas will be recorded by use of a 4-point scale: Pregnancy test: Urinary pregnancy test will be performed at SV2, Visit 3 (Day 28) and at FU2 (if applicable) in

	females of childbearing potential. **Efficacy Assessment** At SV2 and at all on-treatment visits the following will be performed: • Physician´s Global Assessment (PGA) of disease severity on the body and scalp (ranging from "Clear" to "Severe") • Physician´s assessment of the extent and severity of clinical signs of psoriasis vulgaris (redness, thickness and scaliness) • Subject´s Global Assessment of disease severity on the body and scalp (ranging from "Clear" to "Severe") At SV2, Visit 1 and Visit 3 the physician´s assessment of extent of psoriasis (% of total BSA, % of body area and % of scalp area) will be performed. **Patient Reported Outcomes** Four Patient Reported Outcome (PRO) instruments will be used: Subject´s Assessment of Itch, Itch-related Sleep Loss and Children´s Dermatology Life Quality Index (CDLQI) will be collected at Visit 1, Visit 2 and Visit 3 or early withdrawal (if applicable). The Family Dermatology Life Quality Index (FDLQI) will be collected at Visit 1 and Visit 3 or early withdrawal (if applicable).
Primary endpoint	• Adverse events (AEs) • Subjects with serum cortisol concentration of ≤18 mcg/dl at 30 minutes after ACTH-challenge at Week 4 • Change in albumin-corrected serum calcium from baseline (SV2) to Week 4 • Change in calcium excretion from baseline (SV2) to Week 4 in 24-hour urine • Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in 24-hour urine
Secondary endpoint(s)	• Subjects with serum cortisol concentration of ≤18 mcg/dl at both 30 and 60 minutes after ACTH-challenge at Week 4 • Change in calcium:creatinine ratio from baseline (SV2) to Week 4 in spot urine • Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician´s global assessment of disease severity on the body at Week 4 • Subjects with 'treatment success' (i.e., 'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline, 'clear' for subjects with 'mild' disease at baseline) according to the physician´s global assessment of disease severity on the scalp at Week 4 • Percentage change in psoriasis area and severity index (PASI) from baseline (V1) to Week 4 • Subjects with 'treatment success' (i.e., 'clear' or 'very mild) according to the subject´s global assessment of disease severity on the body at Week 4

	• Subjects with 'treatment success' (i.e., 'clear' or 'very mild) according to the subject´s global assessment of disease severity on the scalp at Week 4 • Change in itch as assessed by the Visual Analogue Scale (VAS) from baseline (V1) to Week 4
Statistical methods	The number and percentage of subjects with a serum cortisol concentration ≤18 mcg/dl at 30 minutes, and at both 30 and 60 minutes, after ACTH-challenge at Week 4 will be tabulated. The serum cortisol concentration at time 0 (just before the ACTH challenge) and at 30 and 60 minutes after ACTH-challenge at baseline (SV2) and Week 4, respectively, will be summarised. The number and percentage of subjects experiencing each type of adverse event will be tabulated. For the albumin-corrected serum calcium, calcium excretion in 24-hour urine, calcium:creatinine ratio in 24-hour urine and calcium:creatinine ratio in spot urine, the absolute value by visit and at end of treatment and the change from baseline (SV2) to Week 4 and to end of treatment will be summarised. Furthermore, the 95% confidence interval of mean change from baseline to Week 4 and to end of treatment will be presented. In addition, the parameters will be classified according to the reference range, and shift tables will be produced showing the categories at baseline (SV2) against those at Week 4 and at end of treatment. Summary tables and shift tables will be repeated subgrouped by baseline 25-hydroxy vitamin D classifications. The following will be presented with the 95% confidence interval: • percentage of subjects with 'treatment success' according to the physician's global assessment of disease severity on the body at Week 4 and at end of treatment • percentage of subjects with 'treatment success' according to the physician's global assessment of disease severity on the scalp at Week 4 and at end of treatment • mean percentage change in PASI from baseline (V1) to Week 4 and to end of treatment • percentage of subjects with 'treatment success' according to the subject's global assessment of disease severity on the body at Week 4 and at end of treatment • percentage of subjects with 'treatment success' according to the subject's global assessment of disease severity on the scalp at Week 4 and at end of treatment • mean change in itch as assessed by the VAS from baseline (V1) to Week 4 and end of treatment

For submission to IEC/IRBs and/or regulatory authorities, attach schedule of trial procedures (Section 8.1)

26 Appendix 2: Definitions of Adverse Events and Serious Adverse Events

26.1 Adverse Event Definition

An adverse event is defined as 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)).

This definition includes:

- accidental injuries, events related to trial procedures, reasons for any unfavourable and unplanned change in medication (drug and/or dose), clinically significant worsening of pre-existing conditions, or reasons for admission to hospital or surgical procedures unless these were planned before enrolment. It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the investigational product. In addition, any laboratory abnormality assessed as clinically significant by the (sub)investigator must be recorded as an AE.

26.2 Serious Adverse Event Definition

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. Planned hospitalisation or planned prolonged hospitalisation do not fulfill the criteria for being an SAE but should be documented in the subject's medical record.
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

or

- is a medically important condition. 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 are intensive treatment in an emergency room or at home for allergic broncospasm, blood dyscrasias and convulsions that do not result in hospitalization, development of drug dependency or drug abuse.

27 Appendix 3: Classification of Adverse Events

27.1 Severity

The *severity* of the AE should be described in terms of mild, moderate or severe according to the (sub)investigator's clinical judgement.

Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

If the severity of an AE worsens, a new AE should be recorded.

27.2 Causality

The *causal relation* of the AE to the use of the investigational product should be described in terms of probable, possible or not related 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 the 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 reappear or worsen upon re-challenge. Does not follow a known pattern of response to the investigational product.

27.3 Outcome

The *outcome* of the event should 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 not yet completely resolved.
Not recovered/ not resolved	Event is still ongoing.
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. In case of a SAE, the sequelae should be specified.
Fatal	The subject has died as a consequence of the event. Date of death is recorded as stop date for the AE.
Unknown	Unknown to (sub)investigator, e.g. subject lost to follow-up.

28 Appendix 4: Contact list of LEO, protocol authors, vendors, trial committees and coordinating investigators

Contact details for the international clinical trial manager (ICTM), national lead CRA (NLCRA), medical expert and safety scientist/safety physician are provided to participating trial sites outside the protocol on a list of LEO representatives which is included in clinical trial applications.

Sponsor

LEO Pharma A/S (referred to as 'LEO' in this clinical trial protocol) is the sponsor of the clinical trial:

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2750 Ballerup, DK

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Safety Scientist:

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e-mail: PPD@leo-pharma.com

CRO(s)/vendors

PPD : PPD , PPD , PPD , PPD ; PPD , PPD , PPD , PPD . The CRO will be responsible for all services related to the central laboratory analysis as agreed to in a Service Agreement/Contract. Samples from Eastern and Central Europe will be shipped to and analysed by the UK site, whereas samples from US sites will be shipped to and analysed by the US site.

CCI : CCI , CCI , CCI , CCI , CCI . The CMO will be responsible for the secondary packaging, labelling and distribution of trial medication, and also the receipt, accountability, weighing, reconciliation and destruction of returned trial medication, as agreed to in a Service Agreement/Contract.

Colep Laupheim GmbH & Co. KG: Fockestrasse 12, 88471 Laupheim, Germany. The Contract Manufacturing Organisation (CMO) will be responsible for all services related to the filling of the Investigational Medicinal Product (incl. filling the ointment intermediate into cans and dissolving and dispersing the ointment intermediate in propellants) 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.

PPD : PPD , PPD , PPD , PPD , PPD , PPD . The CRO will be responsible for project management, clinical conduct, data management and monitoring as agreed to in a Service Agreement/Contract.

PPD : PPD , PPD , PPD , PPD , PPD

PPD : PPD , PPD , PPD , PPD , PPD

Coordinating Investigators

International coordinating investigator: Marieke Seyger, MD, PhD, Department of Dermatology, University Medical Centre Nijmegen St Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands, Tel.: +31 24 361 37 24, e-mail: marieke.seyger@radboudumc.nl

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

29 Appendix 5: Subject Assessment of Itch by use of a Visual Analogue Scale (VAS)

Site ID:_____ Subject ID:_____ Date:_____

Subject Assessment of Itch by use of a Visual Analogue Scale (VAS)

Protocol Code Number: **LP0053-1108**
Protocol Title: **Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to < 17 Years) with Plaque Psoriasis**

This assessment will be made by the subject at all treatment phase visits (1-3) and early withdrawal (if applicable).

Do not use this example for the actual assessment; a validated scale of 10 cm must be used.

Instructions for use of Visual Analogue Scale:

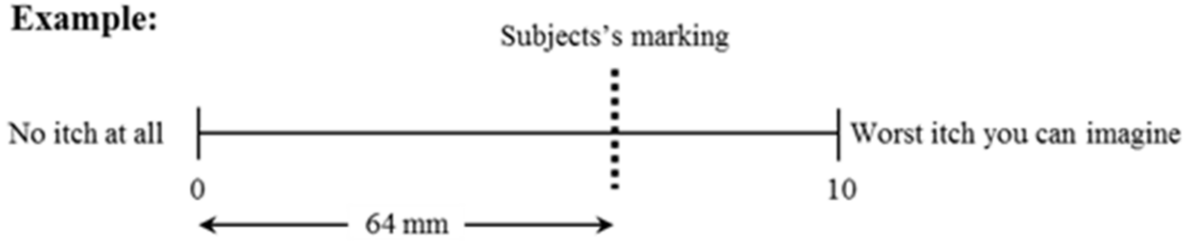
1. Provide the subject with a validated visual analogue scale marked with Subject ID and Visit Number.

2. Ask the subject to rate the **maximal intensity** of itch during the last 24 hours.

3. The subject should mark this with a vertical line on the scale between 0 and 10 (no itch at all and worst itch you can imagine).
4. Collect back the Visual Analogue Scale and include in the study source data.

5. Measure from the left with a ruler and record the distance (in mm) at which the subjects mark crosses the scale. This score (in mm) should be entered into the eCRF.

Example:


Subjects's marking
No itch at all
Worst itch you can imagine
0
10
64 mm

30 Appendix 6: Subject Assessment of Itch-Related Sleep Loss by use ofa Visual Analogue Scale (VAS)

Protocol Code Number: **LP0053-1108**
Protocol Title: **Safety and Effect of LEO 90100 aerosol foam on the HPA Axis and Calcium Metabolism in Adolescent Subjects (Aged 12 to < 17 Years) with Plaque Psoriasis**

This assessment will be made by the subject at all treatment phase visits (1-3) and early withdrawal (if applicable).

Do not use this example for the actual assessment; a validated scale of 10 cm must be used.

Instructions for use of Visual Analogue Scale:

1. Provide the subject with a validated visual analogue scale completed with Subject ID and Visit Number.

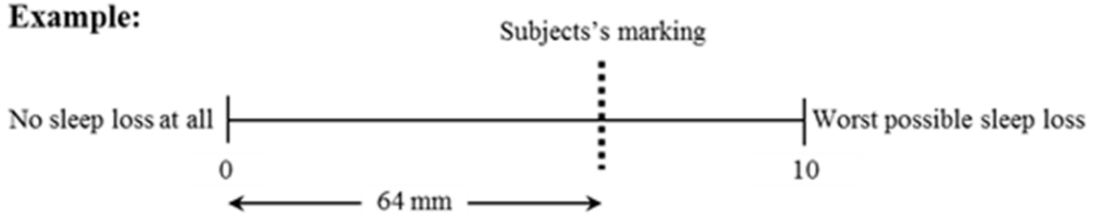
2. Ask the subject to rate the itch-related sleep loss during the last night.

3. The subject should mark this with a vertical line on the scale between 0 and 10 (no sleep loss at all and worst possible sleep loss).

4. Collect back the Visual Analogue Scale and include in the study source data.

5. Measure from the left with a ruler and record the distance (in mm) at which the subjects mark crosses the scale. This score (in mm) should be entered into the eCRF.

Example:



31 Appendix 7: Children's Dermatology Life Quality Index (CDLQI)

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy**, "**scratchy**", **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
7.	Last week, was it **school time?** ⇒ **If school time**: Over the last week, how much did your skin affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒ ❒
	OR		
	was it **vacation time?** ⇒ **If vacation time**: How much over the last week, has your skin problem interfered with your enjoyment of the **vacation**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	❒ ❒ ❒ ❒

Please check that you have answered EVERY question. Thank you.

32 Appendix 8: The Family Dermatology Life Quality Index (FDLQI)

THE FAMILY DERMATOLOGY LIFE QUALITY INDEX (FDLQI)

Respondent's relationship to the subject
(Check (X) ONE only):

☐ (1) Father
☐ (2) Mother
☐ (3) Brother
☐ (4) Sister
☐ (5) Husband/Wife/Partner
☐ (6) Adult child
☐ (999) Other

- The questions relate to the impact of your relative/partner's skin disease on your quality of life over the last month.
- Please read the questions carefully and check one box for each.

1. Over the last month, how much emotional distress have you experienced due to your relative/partner's skin disease (e.g., worry, depression, embarrassment, frustration)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

2. Over the last month, how much has your relative/partner's skin disease affected your physical well-being (e.g., tiredness, exhaustion, contribution to poor health, sleep/rest disturbance)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

3. Over the last month, how much has your relative/partner's skin disease affected your personal relationships with him/her or with other people?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

4. Over the last month, how much have you been having problems with other peoples' reactions due to your relative/partner's skin disease (e.g., bullying, staring, need to explain to others about his/her skin problem)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

5. Over the last month, how much has your relative/partner's skin disease affected your social life (e.g., going out, visiting or inviting people over, attending social gatherings)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

(Please turn over)

6. Over the last month, how much has your relative/partner's skin disease affected your recreation/leisure activities (e.g., vacation, personal hobbies, gym, sports, swimming, watching TV)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

7. Over the last month, how much time have you spent on looking after your relative/partner (e.g., putting on creams, giving medicines, or looking after their skin)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

8. Over the last month, how much extra housework have you had to do because of your relative/partner's skin disease (e.g., cleaning, vacuuming, washing, cooking)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

9. Over the last month, how much has your relative/partner's skin disease affected your work/studies (e.g., need to take time off, not able to work, decrease in the number of hours worked, having problems with people at work)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

10. Over the last month, how much has your relative/partner's skin disease increased your routine household expenditure (e.g., transportation costs, buying special products, creams, cosmetics)?

Not at all/Not relevant ☐ A little ☐ Quite a lot ☐ Very much ☐

Thank you for completing the questionnaire.

33 Appendix 9: Mosteller Formular

In centimeters and kilograms:

$$BSA\ (m^2) = (\ [\ Height\ (cm) \times Weight\ (kg)\ ] / 3600\ )^{\frac{1}{2}}$$

Reference: Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987; 317:1098.

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ELECTRONIC SIGNATURES

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

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Lead, Biostatistical Approval	29-Aug-2016 13:38 GMT+0
PPD	Medical Lead, Medical Approval	29-Aug-2016 15:22 GMT+0