Dermatology beyond the skin

Cover Page

Official title: A phase 3 trial comparing the efficacy and safety of LEO 90100 aerosol foam with the aerosol foam vehicle used twice weekly as long-term maintenance therapy in subjects with psoriasis vulgaris.
LEO Pharma number: LP0053-1004
NCT number: NCT02899962
Date: 12-Apr-2018

Clinical Trial Protocol

LEO 90100 twice weekly maintenance regimen for psoriasis vulgaris

A phase 3 trial comparing the efficacy and safety of LEO 90100 aerosol foam with the aerosol foam vehicle used twice weekly as long-term maintenance therapy in subjects with psoriasis vulgaris.

A 12-month, international, multi-centre, randomised, vehicle controlled, double-blind, 2-arm, parallel group trial.

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:**	**LP0053-1004**
	EudraCT no	**2016-000556-95**
	Date:	**12-Apr-2018**
	Version:	**7.0**

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 , MSc Stat
Biostatistics Lead, Global Clinical Operations

PPD , MD
Medical Lead, Medical Sciences and Safety

PPD , MSc Pharm
Clinical Operations Lead, Global Clinical Operations

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:

Mark Lebwohl, MD
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.

Protocol amendment summary of changes table

Document history

Document	Protocol version	Protocol date	Date of errata sheet
Amendment 6 (non-substantial)	7.0	12-Apr-2018	NA[1]
Amendment 5 (non-substantial)	6.0	22-Aug-2017	25-Aug-2017
Amendment 4 (non-substantial)	5.0	05-Jul-2017	05-Jul-2017
Amendment 3 (substantial)	4.0	14-Dec-2016	22-Dec-2016
Amendment 2 (non-substantial)	3.0	07-Sep-2016	07-Sep-2016
Amendment 1 (substantial)	2.0	19-Aug-2016	22-Sep-2016
Original protocol	1.0	14-Apr-2016	NA

1) According to new company procedures, separate protocol errata sheets are no longer produced. When a protocol is updated, changes since previous version are listed in a protocol summary of changes table located directly before the table of contents.

NA, not applicable.

Protocol amendment summary of changes tables for previous amendments (that is, no. 1 to 5) are provided in Appendix 12.

Amendment 6 (12-Apr-2018)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (38) because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The protocol was updated to clarify how to handle subjects who experience a worsening of psoriasis during the follow-up phase.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has a ~~line through it~~).

Section number and name	Description of change	Brief rationale
Section 3.3.3 Rationale for trial design	The trial will include a screening phase of up to 4 weeks, an open-label treatment phase of 4 weeks, a randomised double-blind maintenance phase of ~~up to~~ 52 weeks, and a follow-up phase of ~~up to~~ 8 weeks.	Clarification that the maintenance phase has a duration of 52 weeks and that the follow-up phase has a duration of 8 weeks.
Section 6.1.1 Overview	This trial is a multi-centre, prospective trial, consisting of an initial open-label treatment phase of 4 weeks followed by a randomised, double-blind, vehicle-controlled, maintenance phase of ~~up to~~ 52 weeks in subjects with psoriasis vulgaris.	
Section 6.1.3 Initial open-label treatment phase	Subjects who achieve treatment success (PGA score of 'clear' or 'almost clear' with at least a 2-grade improvement from baseline) at Visit 2 will be randomised in a ratio of 1:1 in a double-blind fashion to either LEO 90100 or vehicle (maintenance IP) twice weekly for ~~up to~~ 52 weeks.	
Appendix 1 Protocol summary	Methodology: (…) maintenance phase of ~~up to~~ 52 weeks in subjects with psoriasis vulgaris, and an 8-week follow-up period. Duration of treatment: (…) A maintenance phase: randomised treatment (LEO 90100 or vehicle) twice weekly for ~~up to~~ 52 weeks	

Section number and name	Description of change	Brief rationale
Section 3.3.3 Rationale for trial design Section 12.1 Adjudication Committee	The investigators will record all adverse events (AEs), and an independent adjudication panel of ~~dermatologists~~ **2 dermatologists and one endocrinologist** will review all **treatment-emergent** AEs (blinded data) to identify adverse drug reactions of concern associated with long-term topical corticosteroid use. A panel of ~~three~~ **2** dermatologists **and one endocrinologist** ("Adjudication Panel") will review all ~~reported~~ **treatment-emergent** AEs to identify AEs of concern associated with long-term use of topical corticosteroids where a causal relationship between the trial medication and the event is at least a reasonable possibility. **The Adjudication Panel will not review AEs which occurred prior to application of the first dose of IP; this includes AEs reported by screening failures (who per definition did not start open-label treatment).**	Since side effects from steroids may also be endocrine-related, it was decided to include an endocrinologist in the adjudication committee. It has been specified that the Adjudication Panel will only review treatment-emergent AEs.
Section 3.3.3 Rationale for trial design Section 8.12.1 Safety laboratory blood analysis	Therefore, adrenal function testing will be undertaken in a subset of ~~approximately 30~~ randomised subjects with at least moderate psoriasis affecting ~~at least 10%~~ **between 10 and 30%** of the BSA. **The aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure.** Adrenal function testing will be undertaken in a subset of ~~approximately 30~~ randomised subjects with psoriasis affecting ~~more than 10%~~ **between 10 and 30% of the BSA. The aim is to include 25 subjects undergoing HPA axis testing after 52 weeks of exposure.** ~~This means that up to 60 subjects fullfilling the inclusion/exclusion criteria for this part of the trial may need to be enrolled and ACTH tested at Visit 1 and Visit 2.~~	The number of randomised subjects may need to be adjusted to achieve the required exposure data. This will depend on the actual drop-out rate in the trial. It has been specified that subjects undergoing HPA axis testing should have psoriasis affecting between 10 and 30% of the BSA in agreement with inclusion criterion no. 12.

Section number and name	Description of change	Brief rationale
Section 5.3 Safety assessments Section 11.3.8 General principles	Effect on HPA axis (in a subset of subjects with disease involvement ~~>10% BSA~~ **of between 10 and 30% of BSA**), based on serum cortisol ≤18 mcg/dL 30 minutes after cosyntropin injection at Week 4, Week 28, and end of trial (Week 56) or early withdrawal. Furthermore, the inclusion criteria for participating in the HPA axis test are ~~either~~ "Moderate" or "Severe" in the baseline PGA assessment ~~or~~ **and** a baseline BSA ~~of at least 10%~~ **between 10 and 30%**.	It has been specified that subjects undergoing HPA axis testing should have psoriasis affecting between 10 and 30% of the BSA in agreement with inclusion criterion no. 12.
Section 6.1.5 Follow-up phase (FU2)	For subjects undergoing the adrenocorticotropic hormone (ACTH) challenge test, a follow-up visit (Visit FU2) will take place 28 days after the ACTH challenge test performed at the end of treatment **(Visit 15/Early Withdrawal)** if ~~this~~ **the end of treatment** test show~~ed~~ a serum cortisol concentration ≤18 mcg/dl at **both** 30 minutes **and 60 minutes** after ACTH challenge (39, 40). If the results of the ACTH challenge test at Visit FU2 continue to show a serum cortisol concentration ≤18mcg/dl at **both** 30 minutes **and 60 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 **or at 60 minutes** after the ACTH-challenge**, or at both time points**). **Refer to Section 8.12.1 for further details on the ACTH challenge test.**	To avoid overdiagnosing adrenal insufficiency, only subjects with abnormal results at both timepoints after ACTH challenge (30 minutes and 60 minutes) will need to come back to the trial site for additional ACTH challenge tests.
Section 6.1.5 Follow-up phase (FU3)	It has been clarified when the 8-week follow-up phase will start. It has been specified how subjects who experience a worsening of their psoriasis during the follow-up phase should be handled.	Clarification that subjects who leave the trial after the initial treatment period will also need to be followed-up for 8 weeks (in agreement with the definition of rebound [section 11.3.6.2]).

Section number and name	Description of change	Brief rationale
Section 6.2 Sample size	A total of 380 subjects should be randomised in the trial **in order to have power for the primary maintenance treatment objective**. In order to achieve 380 randomised subjects it is estimated that 832 subjects should be included in the trial. **The total number of subjects treated in the trial should also be sufficient to comply with ICH E1 regarding long term safety. The aim is to achieve at least 300 subjects with 26 weeks of exposure and at least 100 subjects with 52 weeks of exposure**. For the HPA axis test, ~~up to 60 subjects (with BSA over 10%) may need to be enrolled to achieve approximately 30 randomised subjects at Visit 2~~ **the aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure**. ~~If among the 380 randomised subjects there are less than 30 subjects undergoing HPA axis testing then the recruitment of subjects for the HPA axis testing will continue until approximately 30 subjects have been randomised for the HPA axis testing.~~The total number of randomised subjects can exceed 380 **in order to achieve a sufficient number of subjects for long-term evaluation of safety and HPA testing**.	The number of randomised subjects may need to be adjusted to achieve the required exposure data. This will depend on the actual drop-out rate in the trial.
Section 16.1 Trial Completion Procedures	This will also include information on when the threshold of 20% of subjects with a 'mild' PGA is reached, and when **a** sufficient number of subjects (~~30 randomised~~ **approximately 25 subjects with 52 weeks of exposure**) have been included in the HPA axis part of the trial.	

Section number and name	Description of change	Brief rationale
Section 6.3 Randomisation	~~The maximum number of subjects to be enrolled with 'mild' disease according to the PGA is capped at 20% to ensure similar distribution of disease severity at baseline as in previous LEO 90100 short-term trials and hence similar trial population.~~	This paragraph has been re-worded and moved to section 10.6; the cap of 20% of mild subjects refers to the population who will be treated with open-label IP, not the randomised subject population (who have already been exposed to 4 weeks open-label treatment).
Section 7.8.3 Restrictions during the trial – follow-up period	**Note that treatment with Enstilar® or IP is not allowed during the follow-up period (Section 6.1.5)**. ~~Otherwise, there are no restrictions on the use of concomitant treatment during the follow-up period.~~	Specification that use of Enstilar® or IP is not allowed during the follow-up period. This sentence was deleted since restrictions may apply to subjects who are in follow-up due to abnormal ACTH test results.
Section 8.1 Schedule of trial procedures	Clarification that the FU3 visit will occur 8 weeks after end of treatment or early withdrawal. A visit window (±4 days) for the FU3 visit has been included.	In the previous version of the protocol, the FU3 visit and any unscheduled visits during the follow-up phase were all described as FU3. A clear distinction has been made between FU3 and unscheduled follow-up visit.
	It has been specified that concomitant medications and concomitant procedures should be recorded at the FU3 visit.	To monitor use of any medication up to the FU3 visit.
	An unscheduled follow-up visit has been included.	To clarify how to handle subjects who experience a worsening of psoriasis during the follow-up phase.
	Footnote no. 19 updated to specify that FU2 visit is only required if end-of-treatment serum cortisol concentration is ≤18 mcg/dl at both 30 minutes and 60 minutes after ACTH challenge test.	To avoid overdiagnosing adrenal insufficiency, only subjects with abnormal results at both timepoints after ACTH challenge (30 minutes and 60 minutes) will need to come back to the trial site for additional ACTH challenge tests.
	Footnotes no. 21 and 22 have been updated to reflect the difference between an unscheduled follow-up visit and the FU3 visit.	To clarify how to handle subjects who experience a worsening of psoriasis during the follow-up phase.
	~~23) After end of treatment visit (Visit 15 or Early Withdrawal) only events of rebound are routinely collected.~~	Footnote deleted since all AEs, including rebound events, will be collected during the whole trial up to the FU3 visit.

Section number and name	Description of change	Brief rationale
	23) Subjects with a serum cortisol concentration ≤18mcg/dl at both 30 minutes and 60 minutes after ACTH challenge at FU2 will be followed up until the adrenal suppression resolves. Further ACTH challenge tests must be captured in the UNS FU page in the eCRF.	Footnote added to remind investigators about the criteria for further follow-up of ACTH subjects. The footnote also describes where such follow-up information should be recorded in the eCRF.
	24) If the subject withdraws prior to completing the initial open-label treatment phase, the ACTH-challenge should not be performed.	Footnote added for clarification in agreement with Section 8.12.1.
	25) Only required if last FU3 is performed at the trial site	Footnote added to clarify that certain investigator assessments at FU3 are only required if the visit is performed at the trial site.
Section 8.12.1 Safety laboratory blood analysis	If ~~the result of~~ the ACTH challenge test at Visit 15 (end of maintenance phase~~),~~ or at early withdrawal~~)~~ shows a serum cortisol concentration ≤18 mcg/dl at **both** 30 minutes **and 60 minutes** after the ACTH challenge, a further ACTH challenge test is required 4 weeks later **(FU2 visit)**. If the results of the ACTH-challenge test at ~~this visit~~ **the FU2 visit** continue to show a serum cortisol concentration ≤18mcg/dl at **both** 30 minutes **and 60 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 **or at 60 minutes** after the ACTH challenge, **or at both time points**). **The data from such further ACTH challenge tests must be captured in the unscheduled follow-up visit page in the eCRF.**	To avoid overdiagnosing adrenal insufficiency, only subjects with abnormal results at both timepoints after ACTH challenge (30 minutes and 60 minutes) will need to come back to the trial site for additional ACTH challenge tests. It has been specified where to capture data from further ACTH challenge tests.
Section 8.12.1 Safety laboratory blood analysis	~~After this~~ **Within 10 minutes after blood sampling**, CORTROSYN® / Synacthen® ~~is~~ **will be** injected, as described in section 10.9.	A time window for the injection of CORTROSYN® / Synacthen® has been specified to clarify the procedure.

Section number and name	Description of change	Brief rationale
Section 9.1 Collection of adverse events	AEs**, including events of rebound,** must be collected from time of first trial-related activity after the subject has signed the informed consent form until the ~~end of treatment~~ **FU3 visit.** ~~Events of rebound will be collected during the follow-up period to end of trial~~. **Refer to section 11.3.6. 2 for a definition of rebound.**	To clarify that rebound events will be collected during the whole trial up to the FU3 visit.
Section 9.5 Follow-up for Final Outcome of Adverse Events	Once a subject has completed the ~~treatment phases of the trial~~ **FU3 visit**, AEs classified as possibly or probably related to the IPs should be followed for 14 days or until the final outcome is determined, whichever comes first.	To clarify that related AEs will be followed up from the FU3 visit rather than from end of treatment.
Section 10.6 Treatment assignment	~~A cap on the number of subjects with 'mild' disease according to the PGA is set at 20%.~~ **The maximum number of subjects to be included in the open-label phase with 'mild' disease according to the PGA at baseline (visit 1) is capped at 20% to ensure similar distribution of disease severity at baseline as in previous LEO 90100 short-term trials and hence similar trial population.**	Clarification that the cap of 20% of mild subjects refers to the baseline population who will be treated with open-label IP, not the randomised subject population (who have already been exposed to 4 weeks open-label treatment).
10.9.1 CORTROSYN® and Synacthen®	Table 15: ~~Ampoules: 10 times 1 ml~~ **1 ml ampoules**	Pack size corrected.

Section number and name	Description of change	Brief rationale
Section 11.1 Determination of sample size	~~Recruitment will be stopped when 380 subjects are randomised. However, if among the 380 randomised subjects there are less than 30 subjects undergoing HPA axis testing then the recruitment of subjects for the HPA axis testing will continue until approximately 30 subjects have been randomised for the HPA axis testing. The total number of randomised subjects can exceed 380.~~ **For the HPA axis testing, the aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure.** **The total number of subjects treated in the trial should also be sufficient to comply with ICH E1 regarding long term safety. The aim is to achieve at least 300 subjects with 26 weeks of exposure and at least 100 subjects with 52 weeks of exposure.** All randomised subjects have been exposed for 4 weeks during the open-label treatment phase. During the maintenance phase with 380 randomised subjects, assuming an exponential decline and a drop-out rate of 30% over 52 weeks, we can expect to have 326 subjects exposed for 22 weeks and 273 subjects exposed for 48 weeks. This means that we will have 326 subjects exposed for a total of 26 weeks, and 273 subjects exposed for a total of 52 weeks. **If the actual drop out rate is higher than the assumed drop out rate of 30%, more subjects will be recruited and randomised to achieve at least 380 randomised subjects, including at least 300 subjects with 26 weeks of exposure and at least 100 subjects (including approximately 25 subjects undergoing HPA axis testing) with 52 weeks of exposure.** **Recruitment will be stopped when a sufficient number of subjects are randomised in order to obtain the above, considering the observed randomisation and drop-out rates.**	The number of randomised subjects may need to be adjusted to achieve the required exposure data. This will depend on the actual drop-out rate in the trial.

Section number and name	Description of change	Brief rationale
Section 12.1 Adjudication Committee	The (sub)investigator assessment of causal relationship of the use of trial medication to the event, location of cutaneous events, **severity**, and seriousness.	It has been specified that the Adjudication Panel will also review the severity of the treatment-emergent AEs.
Appendix 6 Contact list	List of protocol authors have been removed. The 3 members of the Adjudication Panel have been listed.	A protocol may have multiple authors during its life-cycle. A log of all protocol authors is kept at LEO. 2 dermatologists and one endocrinologist have now been contracted to the Adjudication Panel.
Appendix 12 Protocol amendment history	New appendix.	To provide overview of the changes to the protocol.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

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2 Trial Identification

EudraCT number: 2016-000556-95

IND number: 114063

3 Introduction and Rationale

3.1 Psoriasis vulgaris

Psoriasis is an inflammatory skin disease that occurs in approximately 2% of the worldwide population (1, 2). In addition to skin manifestations, psoriasis is associated with multiple co-morbidities e.g. arthritis and cardiovascular disease (3, 4). The hallmark of psoriasis is inflammation of the skin as a result of excessive response to danger signals. 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 (3, 5, 6). Skin lesions can be painful, pruritic and may cause significant emotional and physical discomfort (7, 8).

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 as adjunct to either phototherapy, systemic or biologic agents (9, 10). One of the advantages of topical therapies is a reduced risk of systemic toxicity compared to other treatment modalities.

Psoriasis is a life-long disease for most patients and there is a need for a safe long-term treatment strategy. When psoriasis treatment is discontinued, lesions will likely recur. Optimal management of psoriasis must therefore include a strategy for initial rapid relief of symptoms as well as a long-term strategy to maintain remission.

3.2 Experience with Investigational Product

LEO 90100 aerosol foam (referred to as LEO 90100) is a combination product developed for the topical treatment of psoriasis vulgaris. It contains calcipotriol 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate). LEO 90100 is packed in an aluminium can with dimethyl ether (DME) and butane propellants. The propellants evaporate quickly after application leaving a foam on the skin surface.

LEO 90100 is available on the market in United Stated (US) and the European Union (EU) (under the trade name Enstilar® foam) for treatment of psoriasis vulgaris for up to 4 weeks.

The clinical efficacy and safety of LEO 90100 has been documented in vehicle- and active comparative trials of 4 weeks duration. Three controlled safety and efficacy trials involving more than 900 subjects, which formed the basis for marketing approval, demonstrated that LEO 90100 is highly efficacious for the treatment of adult patients with psoriasis vulgaris over a 4-week period. The data showed that LEO 90100 is a more efficacious treatment option than calcipotriol plus betamethasone dipropionate (calcipotriol/BDP) ointment and the individual active ingredients, based on investigator-assessed treatment success and the proportion of subjects achieving at least 75% improvement in Psoriasis Area and Severity Index (PASI; PASI75). LEO 90100 was well tolerated, with a safety and tolerability profile comparable to calcipotriol/BDP ointment and the individual active ingredients. Furthermore, a maximum use systemic exposure trial in subjects with moderate to severe extensive psoriasis found no clinically relevant impact on the Hypothalamic-Pituitary-Adrenal (HPA) axis or calcium homeostasis after 4 weeks of treatment with LEO 90100 (mean amount administered 62 g/week versus approximately 30 g/week in the other 4 week trials).

Data supporting the safety and efficacy of LEO 90100 for up to 12 weeks are derived from a 12-week safety and efficacy trial in 460 subjects with psoriasis vulgaris (Trial LP0053-1003), which compared LEO 90100 to calcipotriol/BDP gel. This trial showed that prolonged treatment for up to 12 weeks led to continued improvement in disease severity in both the LEO 90100 and calcipotriol/BDP gel arms, with improvement being more pronounced in the LEO 90100 arm. The treatment with LEO 90100 for up to 12 weeks was not associated with any new safety findings compared to 4 weeks treatment; the safety profile of LEO 90100 over 12 weeks was similar to that of calcipotriol/BDP gel over 12 weeks. These data, together with the data from the 4-week controlled safety and efficacy trials, highlighted that the superior efficacy of the foam is achieved without compromising tolerability.

Further information regarding LEO 90100 relevant to clinical trials can be found in the Investigator's Brochure (IB) (11).

3.3 Trial Rationale

3.3.1 Background

While data is available from trials of 4-week and 12-week duration supporting the efficacy of LEO 90100 in clearing psoriasis, long-term safety and treatment strategies utilizing LEO 90100 for long-term disease management have not been investigated. The aim of this trial is to evaluate the use of LEO 90100 for maintenance therapy and to document long-term safety and efficacy. The goal of a maintenance treatment would be to prolong remission as long as possible while minimising adverse effects.

Various regimens using corticosteroids as monotherapy or in combination with a non-steroidal agent such as vitamin D analogue or ammonium lactate have been evaluated for maintenance of response (12, 13, 14, 15, 16). The results show that approaches utilising alternating weekend and weekday treatment are effective and safe. However, they involve the use of multiple products on different days which may be challenging for a patient in terms of adherence to treatment. Therefore, a maintenance regimen which uses a single fixed-combination product could simplify treatment. There is evidence to suggest that twice weekly intermittent use of calcipotriol/BDP combination gel is effective in maintaining efficacy and reducing relapse rate compared to as needed use on the scalp (16). Based on these observations, twice-weekly use of LEO 90100 for maintenance of response would provide a simple and convenient regimen, which could contribute to patient adherence. The use of only one product for both clearance and maintenance treatment, and just adjusting the frequency of application, would be expected to contribute to patient acceptance, compliance and thereby successful outcomes.

3.3.2 Research hypothesis

The present trial will evaluate the efficacy and safety of LEO 90100 used as a long-term twice-weekly maintenance therapy compared with vehicle. Following an initial 4-week period where all subjects will be treated with LEO 90100 in accordance with the currently approved labeling, they will be randomised to receive either LEO 90100 or vehicle per the twice weekly maintenance regimen for 52 weeks. In cases of relapse, affected subjects in either treatment group will again receive LEO 90100 to apply once daily for 4 weeks on active areas on trunk and limbs. Thus, the vehicle arm will also utilise re-treatment as needed, similar to the use in clinical practice for the licensed calcipotriol/BDP products. Thus, the trial will compare two ways of using LEO 90100: a proactive approach with fixed twice-weekly maintenance regimen with a conventional, reactive approach. The research hypothesis is that the proactive twice-weekly maintenance use of LEO 90100 will prolong the time to relapse and reduce the frequency of relapses in subjects with psoriasis vulgaris, as compared with vehicle while still maintaining a favorable safety profile. It is further hypothesized with regard to long-term efficacy that subjects who receive LEO 90100 twice weekly will demonstrate superior response to those randomised to receive vehicle, as measured by the number of days in remission.

3.3.3 Rationale for trial design

Overall design and treatment duration

The trial will include a screening phase of up to 4 weeks, an open-label treatment phase of 4 weeks, a randomised double-blind maintenance phase of 52 weeks, and a follow-up phase of 8 weeks.

In the initial open-label phase, all subjects will receive treatment with LEO 90100 once daily for 4 weeks. The purpose of this initial period of daily treatment is to allow clearance ("treatment success") of the psoriatic lesions so that subjects will enter the maintenance phase in a symptom-free state. Treatment success is defined as a Physician's Global Assessment of disease severity (PGA) score of 'clear' or 'almost clear' with at least 2-grade improvement from baseline.

In the maintenance phase, subjects will be randomised to receive twice weekly treatment with either LEO 90100 or vehicle (maintenance investigational product [maintenance IP]). At relapse (defined as a PGA score of at least 'mild'), both treatment groups will receive LEO 90100 (rescue investigational product [rescue IP]) to apply once daily on affected areas on trunk and limbs, with the purpose of regaining the disease control. Subjects will be treated for 4 weeks with rescue IP on areas with active psoriasis, and will be instructed to also treat any additional areas that may become active during this 4-week period with rescue IP. During relapse subjects will continue twice weekly treatment with maintenance IP on areas that are not active. Subjects who do not achieve 'clear' or 'almost clear' according to the PGA after 4 weeks will exit the trial. A duration of 12 months for the maintenance phase was chosen as it allows an assessment of prevention of relapse over a period of time during which relapse would be expected to occur on a regular basis. A 12-month duration will allow assessment of the frequency of relapses and the number of days in remission, which are important parameters in the assessment of utility of long-term maintenance therapy.

Importantly, the maintenance treatment duration of 12 months following 4 weeks of initial, once daily treatment is considered appropriate to obtain adequate data on the long-term safety and efficacy of LEO 90100.

Frequency of applications during the maintenance phase and drug amount

Data from several small trials with intermittent use of topical corticosteroids indicate that twice-weekly application on weekends is an effective and safe regimen. The twice-weekly regimen used in this trial with 3 or 4 days between applications has been selected based on a

discussion with a panel of dermatologists. This regimen is justified by published data and in-house studies as outlined below. There is broad consensus in the literature that the stratum corneum can act as a reservoir for topically applied drugs and that this can reduce the frequency of applications (17). The effect of clobetasol propionate applied topically on rabbit skin was studied by Abidi et al. (18) who concluded that a single dose maintained full anti-inflammatory effect for 4 days. Proprietary data on calcipotriol/BDP combination products suggest that the half-life in the skin is approximately 3 days (19, 20). These data support the effectiveness of a twice-weekly regimen with 3 or 4 days between applications.

The maximum allowance of maintenance IP during maintenance phase is set at 3 cans (3 x 60 g) for 4 weeks. This ensures that subjects will have sufficient maintenance IP to use up to 15 g/day (maximum daily dose according to the product labeling) twice weekly during each 4-week period. Note that due to the visit window of +/- 4 days, subjects may need up to 9 applications during a 4-week period. This amount is considered adequate as 15 g is sufficient to cover more than 30% of body surface area (BSA), and it is supported by previous experience from LEO 90100 clinical trials where subjects with extensive psoriasis (15-30% of BSA) used on average 9 g per day, and subjects in short–term efficacy and safety trials used on average less than 5 g.

Subjects

In order to qualify for the trial, subjects must meet the inclusion/exclusion criteria, which are designed to select a population that is representative for the target population and are consistent with the criteria used in the short-term pivotal trials in psoriasis vulgaris; i.e., subjects of all disease severities amenable to topical therapy, with psoriasis lesions on the trunk and/or limbs involving between 2-30% of BSA. The eligibility criteria are selected to prevent any confounding issues with diagnosis and minimize any possible effect of concurrent diseases or concomitant medications on clinical assessment.

Assessments and endpoints

Clinical assessments including PGA, assessment of severity of a target lesion/location, signs and extent of psoriasis (to calculate PASI) will be obtained by trial investigators at each trial visit. Subjects will be required to complete a self-assessment of disease severity as well as quality of life questionnaires, and to capture psoriasis symptoms using the Psoriasis Symptom Inventory (21, 22) on a regular basis during the trial.

The primary endpoint will be the time to first relapse. Relapse is defined as a PGA score of at least ‘mild’, i.e., worsening of psoriasis from ‘clear’ or ‘almost clear’ (a score required for

entering the maintenance phase) to the same level of disease severity as required at study entry, thus necessitating the re-initiation of once daily treatment on the active area(s). The secondary endpoints, the number of relapses and the number of days in remission ('clear' or 'almost clear'), are considered to be clinically meaningful.

One of the safety endpoints is the rebound phenomenon. Rebound may signify a severe deterioration of psoriasis that is significantly worse than before the treatment was initiated or a change in the character of the psoriasis (e.g., from plaque to pustular form), or both. Per the Committee for Human Medicinal Products (CHMP) guideline on clinical investigation of medicinal products indicated for treatment of psoriasis (23), rebound is defined as "worsening of psoriasis over baseline value (e.g. PASI>125%) or new pustular, erythrodermic or more inflammatory psoriasis occurring within 2 months of stopping therapy. A simple worsening of psoriasis beyond 2 months of therapy may represent the natural course of the disease (relapse) rather than a rebound associated with drug". The National Psoriasis Foundation Medical Advisory Board (US) has also proposed a standard definition of rebound (24). Rebound is said to occur if the PASI is 125% or greater than baseline, or if new generalized pustular, erythrodermic or more inflammatory psoriasis occurs within 3 months of stopping therapy. However, these definitions may not be optimal in patients with mild disease, with low PASI, where even a minor worsening in disease severity may fulfill the criteria for PASI >125%, without in fact being a severe and sudden worsening which is characteristic of rebound. Therefore, for the purpose of this trial, rebound will be defined as (i) an m-PASI ≥12 AND an increase in m-PASI of ≥125% of the baseline value, or (ii) new pustular, erythrodermic or more inflammatory psoriasis either a) within 2 months after discontinuation of once-daily treatment in the initial open-label phase, b) within 2 months after discontinuation of once-daily relapse treatment, or c) within 2 months after end of maintenance treatment (up to Visit FU3). Hence, only psoriasis that becomes considerably worse than it has previously been will be considered as rebound.

Assessment of target lesion/location is included as a complement to the PGA to capture information on severity of individual signs, i.e. redness, thickness and scaliness of target plaques. To document the development of response over time, target lesion/location photographs will be taken in a subset of patients recruited at one or a few selected sites equipped with adequate photographic equipment. Subjects will need to give a separate written consent for the collection of photographs. Even if they do not accept the collection of photographs, they may still participate in the main part of the trial.

One of the main objectives of this trial is to investigate the long-term safety of LEO 90100 over 56 (4 + 52) weeks, especially to evaluate the risk of corticosteroid-related cutaneous

adverse reactions and possible systemic effect during prolonged or repeated use of the product. The investigators will record all adverse events (AEs), and an independent adjudication panel of 2 dermatologists and one endocrinologist will review all treatment-emergent AEs (blinded data) to identify adverse drug reactions of concern associated with long-term topical corticosteroid use.

Because of the potential effect of vitamin D analogue containing products on calcium metabolism, there will be safety analyses of the parameters of calcium metabolism from blood and urine samples. As in previous LEO 90100 safety and efficacy trials, albumin-corrected serum calcium and spot urine calcium-creatinine ratio will be analysed in samples collected at baseline, Week 4 and at the end of trial.

Laboratory evidence of adrenal insufficiency due to the use of topical corticosteroid treatment has been reported, however, physiologic adrenal suppression is a common occurrence of little clinical significance (25). Pathologic adrenal suppression from topical corticosteroid use is a very rare occurrence; after nearly half a century of world-wide topical steroid use, there is only a few clinical cases describing prolonged corticosteroid-induced pathological adrenal suppression (25). Furthermore, these cases occurred in adults using at least two times the maximum recommended dose of super-potent corticosteroids for as long as 18 months or, in the single case that did not exceed this dosage, involved continuous use for 5 years. It is not considered to be ethically justified to perform adrenal function testing on all patients in the present trial, as the risk of clinical adrenal insufficiency with the use of topical corticosteroids is low and such testing involves an invasive technique. Therefore, adrenal function testing will be undertaken in a subset of randomised subjects with at least moderate psoriasis affecting between 10 and 30% of the BSA. The aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure. The testing will be done at selected trial sites using the ACTH stimulation test. The proposed sample size is in line with the typical sample size for trials evaluating effect of topical corticosteroids on the HPA axis function (26) and also a previous recommendation by the US Food and Drug Agency (FDA) for a maximum use systemic exposure trial (LEO 90100-30). Testing will be done at baseline, at the end of the initial open-label phase (Week 4), at Week 28, and at the end of trial (Week 56 or at early withdrawal).

Subjects will need to give a separate written consent for having ACTH challenge tests performed. If they do not agree to the having ACTH challenge tests performed, they may still participate in the main part of the trial.

Local safety and tolerability will be evaluated by the scoring of application site skin reactions using the same assessment as used in the short-term trials with LEO 90100. Clinical signs and symptoms will be assessed on a 4-point scale (from absent to severe). Perilesional erythema, oedema, dryness, and erosion will be assessed by investigator and application site burning or pain will be assessed by subject.

To support clinical decision-making when treating psoriasis patients, it is important to consider quality of life. Therefore, evaluation of quality of life is included in this trial by means of the generic EQ-5D-5L-PSO questionnaire, the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment: Psoriasis questionnaire (WPAI:PSO). The EQ-5D-5L-PSO is a standardised instrument for use as a measure of health outcome. DLQI is a validated dermatology specific questionnaire, which measures specific factors influencing the quality of life for patients with skin disease. WPAI:PSO is a questionnaire which assesses the impact of psoriasis on patients' ability to work and perform regular activities. These questionnaires will complement the physicians' assessments to obtain a more complete understanding of the subject's disease status and potential changes during this trial.

A Psoriasis Symptom Inventory (PSI) is included to assess the severity of psoriasis symptoms throughout the induction (open-label) and the maintenance phase. It is anticipated that the symptom diary data recorded on a weekly basis will provide a more sensitive measure of the effect of maintenance treatment than the monthly assessments of the PGA by investigators.

Concomitant treatments

During the course of the trial, subjects must not use any concomitant treatments that have a possible effect on psoriasis vulgaris on the treatment areas (trunk and/or limbs). This includes various systemic treatments (e.g. systemic corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants and biological therapies) as well as topical treatments. Use of any drug except the IP for the treatment of psoriasis vulgaris is prohibited on the treatment areas, only emollients are allowed (but only on days when IP is not being applied).

As LEO 90100 contains a potent steroid, it is not allowed to be used on the face, axillae, and groin. Only mild steroids or non-steroidal products will be allowed on these areas.

As the purpose of this trial is to evaluate the efficacy of maintenance treatment on the body, subjects with severe or extensive scalp psoriasis requiring treatment with potent or superpotent steroids will be excluded.

A stable concomitant treatment regimen (no start or change of dosage during the trial) with drugs that have a potential effect on psoriasis (e.g., beta blockers, anti-malarials, angiotensin-converting enzyme (ACE) inhibitors and lithium) is allowed during the trial. Although these drugs have a potential effect on psoriasis, they are not known to cause fluctuations in disease severity and therefore should not affect the subject's response to trial medication.

Prior to randomisation, a washout period should be completed if the subject is treated, or has recently been treated with anti-psoriatic treatments or other relevant medication that could influence the outcome of the trial. Additional restriction apply for subjects participating in the HPA axis test.

Biomarkers

Psoriasis is an immune mediated inflammatory skin disease and is associated with serious morbidities, such as cardiovascular disease, diabetes, depression and psoriatic arthritis. Potential biomarkers related to inflammation, cardiovascular disease and metabolic syndrome have been identified. In patients with severe psoriasis responding to systemic therapy, biomarkers of cardiovascular disease have been demonstrated to improve (27). In this trial, a panel of serum biomarkers is being investigated in order to assess inflammation and cardiovascular risk. Blood samples will be taken at baseline, at Week 28, and at the end of treatment (for patients who have completed at least 40 weeks of the trial from baseline) in a patient population with 'mild' to 'severe' disease treated with topical therapy.

Subjects will need to give a separate written consent for the collection of these blood samples. If they do not agree to the collection of samples for this purpose, they may still participate in the main part of the trial.

3.4 Ethical Considerations

Psoriasis vulgaris is a chronic disease requiring long-term therapy for most patients. Various formulations of topical corticosteroids, topical vitamin D analogues and their combination have been shown to provide safe and effective initial therapy to achieve clearance of the lesions. However, disease signs usually recur within a few months after discontinuation of treatment in the majority of patients (28) .

LEO 90100 is a combination product of calcipotriol 50 mcg/g and betamethasone 0.5 mg/g (as dipropionate). Long-term safety of both active components of LEO 90100, used individually or in combination, has been well documented. Long-term studies of calcipotriol have shown that it is well tolerated with few adverse effects (29, 30). The local adverse effects

of calcipotriol are related to skin irritation, including burning, itching, and erythema. With the exception of skin irritation, side effects of topical calcipotriol are usually minimal; the risk of hypercalcemia/hypercalciuria is low when the drug is used appropriately.

The long-term use of products containing potent or super-potent topical corticosteroids can have a multitude of adverse cutaneous side effects, such as skin atrophy, telangiectasia, striae and tachyphylaxis. Systemic reactions due to topical use of corticosteroids are rare in adults, however, they can be severe. Adrenocortical suppression, cataract, infection, impaired glycaemic control of diabetes mellitus, and increase of intra-ocular pressure can occur, especially after long-term treatment of large areas and/or with doses exceeding recommended doses. Therefore, intermittent maintenance treatment is a commonly recommended approach for corticosteroids to control the signs of psoriasis while reducing drug exposure and thereby the risk for adverse effects (31).

LEO 90100 (calcipotriol 50 mcg/g plus betamethasone 0.5 mg/g [as dipropionate]) has proved to be a highly effective and well tolerated treatment for psoriasis vulgaris with a favourable benefit/risk profile when used for 4 and up to 12 weeks (11), but no long-term trials or investigations of the risk of skin atrophy or duration of remission and risk of rebound have been conducted.

The long-term use of repeated courses of the calcipotriol/BPD combination has been investigated with the ointment and gel formulation (Daivobet® ointment and Daivobet® gel), and demonstrated to provide safe, efficacious management of psoriasis of the body and scalp over the course of one year (32, 33). The treatment did not appear to be associated with a higher incidence of corticosteroid-related AEs during the long-term therapy than calcipotriol-based regimens.

The purpose of the present trial is to investigate if LEO 90100 can be used by patients to provide safe and efficacious long-term management of psoriasis. In particular, the trial will investigate whether twice weekly applications of LEO 90100 is able to maintain the initial clinical efficacy for a longer period of time as compared to twice weekly application of vehicle. Since both treatment groups will receive LEO 90100 once daily for 4 weeks in case of relapse, the vehicle arm will utilise re-treatment as needed and thus reflect normal clinical use of the product (i.e., 4 weeks courses of once daily treatment upon re-occurrence of active lesions). This means that also subjects in the vehicle arm will be provided with medication effective in the treatment of psoriasis.

Comparisons of safety data between LEO 90100 and the two other marketed formulations show that the systemic safety profile and short-term AE profile of LEO 90100 are similar to those of calcipotriol/BDP ointment and calcipotriol/BDP gel, and no new safety concerns have emerged for LEO 90100 beyond those already described for the calcipotriol/BDP combination product in the ointment and gel formulations. Based on the fact that the potency of LEO 90100 is only moderately increased when compared to Daivobet® ointment, with no enhanced systemic effects, and the short-term safety profiles of the two formulations are similar, no specific safety or tolerability concerns are anticipated with the proposed long-term treatment.

Subjects participating in the trial will be under careful supervision of a dermatologist or general practitioner experienced in Good Clinical Practice (GCP) clinical trials and in the handling of psoriasis vulgaris during the entire course of the trial and will be required to attend planned trial visits every 4 weeks as well as unscheduled visits in case of relapse. At either their own, or the physician's discretion, subjects may be withdrawn from the trial at any time.

Overall, the expected benefits related to long-term therapy outweighs the anticipated risks and inconvenience for the participating subjects.

4 Trial Objectives

4.1 Primary Objective

The primary objective is to evaluate the efficacy of a twice weekly maintenance regimen with LEO 90100 compared to vehicle in the prevention of relapse in subjects with psoriasis vulgaris.

4.2 Secondary Objectives

- To evaluate the long-term efficacy (up to 52 weeks) of LEO 90100 used twice weekly as maintenance therapy compared to vehicle in subjects with psoriasis vulgaris
- To evaluate the long-term safety of LEO 90100 (up to 52 weeks) in subjects with psoriasis vulgaris

4.3 Exploratory Objective

- To evaluate the effect of long-term treatment on biomarkers of inflammation and cardiovascular disease (this part of the trial is optional and will be reported separately from the clinical trial report).

5 Trial Endpoints

5.1 Primary Endpoint(s)

- Time to first relapse (at least 'mild' according to the PGA).

5.2 Secondary Endpoints

- Number of days in remission ('clear' or 'almost clear' according to the PGA) during the maintenance phase
- Number of relapses during the maintenance phase.

Other endpoints planned to be analysed in this trial can be found in section 11.3.4.

5.3 Safety assessments

- Adverse events of concern associated with long-term corticosteroid use
- Incidence of rebound (as defined in section 11.3.6.2)
- Local safety and tolerability assessment scores
- Effect on calcium metabolism, based on change from baseline in serum calcium and spot urinary calcium at Week 4 and the end of trial
- Effect on HPA axis (in a subset of subjects with disease involvement of between 10 and 30% of BSA), based on serum cortisol ≤18 mcg/dL 30 minutes after cosyntropin injection at Week 4, Week 28, and end of trial (Week 56) or early withdrawal.

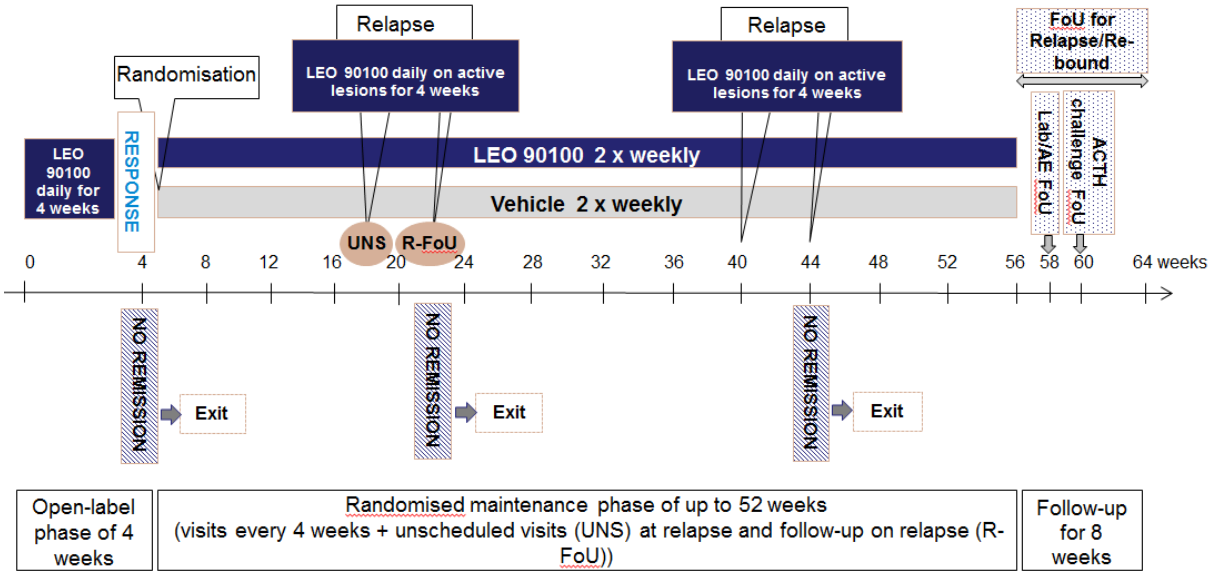
Exposure and standard safety data will be reported as described in sections 11.3.3 and 11.3.6.

6 Trial Design

6.1 Overall Trial Design

The overall trial design is illustrated in Figure 1 below.

Figure 1 Trial Design



6.1.1 Overview

This trial is a multi-centre, prospective trial, consisting of an initial open-label treatment phase of 4 weeks followed by a randomised, double-blind, vehicle-controlled, maintenance phase of 52 weeks in subjects with psoriasis vulgaris.

After the screening phase, subjects deemed eligible for the trial (adults with psoriasis vulgaris on the trunk and/or limbs rated as at least ‘mild’ according to the PGA, BSA 2-30% and m-PASI of at least 2) will be enrolled to the initial open-label phase, where they will apply LEO 90100 once daily on the psoriatic lesions on trunk and/or limbs for 4 weeks.

- Subjects who achieve treatment success (PGA score of ‘clear’ or ‘almost clear’ with at least a 2-grade improvement from baseline) at Week 4 will be randomised in a 1:1 ratio to a maintenance phase of 52 weeks with LEO 90100 or vehicle (maintenance IP) twice weekly.
- Subjects who do not achieve treatment success after 4 weeks of once daily treatment (i.e., non-responders) will be discontinued from the trial.

During the randomised maintenance phase, subjects will apply maintenance IP twice weekly 3 or 4 days apart (fixed days) on all areas on the trunk and limbs where lesions have cleared or almost cleared after the initial open-label phase or after relapse treatment. Subjects will be assessed regularly at clinical visits (every 4 weeks). In addition, if in the opinion of the

subject, a relapse (exacerbation of psoriasis) has occurred between two regular monthly visits, the subject will be assessed by the investigator at an unscheduled visit.

Following confirmation of a relapse the subject will be provided with rescue IP and will be asked to apply it to the active area(s) on trunk and/or limbs, irrespective of whether those areas were active at baseline or they are new lesions. The rescue IP is to be applied once daily on the active areas for 4 weeks. (Note: This treatment is referred to as 'relapse' or 'rescue' treatment). If additional areas become active during rescue treatment, these should also be treated once daily with rescue IP. During a relapse, areas that are not active will continue twice weekly maintenance treatment.

- If a score of 'clear'/'almost clear' according to the PGA is regained after 4 weeks, the twice weekly maintenance regimen will be re-started on the now 'clear'/'almost clear' area(s) according to the original randomisation scheme (for details see section 6.1.4).
- If a score of 'clear'/almost clear' according to the PGA is not regained after the 4 weeks of once daily rescue treatment, the subject will exit the trial.

A detailed description of each phase is provided in the section below.

Planned date of enrolment of first subject: Q1-2017
Planned date of completion of last subject: Q3-2019
Estimated number of trial sites and country allocation: Approximately 58 sites in Canada, France, Germany, Poland, United Kingdom and United States.

6.1.2 Screening/Washout Phase

Prior to performance of any trial related procedure (including washout), signed informed consent must be obtained from the subject.

A washout period will have to be completed for subjects who are or have recently been treated with anti-psoriatic treatments or other relevant medication not permitted as defined by the exclusion criteria (see Section 7.3). The washout is to ensure that no other treatment could interfere with the response obtained with the IPs in the trial. The duration of the washout period is limited for logistical reasons to a maximum of 4 weeks. Because the maximum washout is 4 weeks, subjects who have recently been treated with biologics that require more than a 4 week washout period (e.g. ustekinumab should not be used for 16 weeks prior to commencing the trial), will not be eligible for the trial unless they have been off- treatment for several weeks (e.g. at least 12 weeks for ustekinumab) prior to the eligibility evaluation.

Assessment of subject eligibility should be made at a Screening Visit, prior to commencing a washout period. Screening assessments and trial procedures to be performed at Screening Visit are outlined in Section 8. On completion of the washout period, confirmation of the subject's ongoing eligibility for the trial will be made at Visit 1.

However, if no washout is needed the subject can enter Visit 1 directly.

6.1.3 Initial open-label treatment phase

Eligible subjects will first enter an initial open-label treatment phase, where they will be instructed to apply LEO 90100 once daily on the psoriatic lesions on trunk and limbs for 4 weeks. All trial medication needed for 4 weeks (7 cans of LEO 90100) will be dispensed at Visit 1.

The first application of the trial medication should be made at Visit 1 under the supervision and instruction of the trial staff or at home on the same day the subject attended Visit 1. For detailed treatment instructions, see section 10.2.

After 4 weeks, subjects will be asked to return to the trial site for clinical evaluation and medication accountability (Visit 2). All trial medication dispensed at Visit 1 will be collected.

Subjects who achieve treatment success (PGA score of 'clear' or 'almost clear' with at least a 2-grade improvement from baseline) at Visit 2 will be randomised in a ratio of 1:1 in a double-blind fashion to either LEO 90100 or vehicle (maintenance IP) twice weekly for 52 weeks.

The randomisation of subjects will be stratified by trial site, HPA axis testing, and by baseline disease severity, as determined by the PGA at Visit 1.

Randomised subjects will receive the supply of maintenance IP for 4 weeks and will be instructed on how to apply it during the maintenance phase and what to do in case of relapse.

Subjects who do not achieve treatment success after this initial open-label treatment phase will exit the trial.

6.1.4 Maintenance phase

During the maintenance phase, subjects will apply the randomised maintenance IP twice weekly on trunk and limbs to the areas where lesions have cleared or almost cleared after treatment was initiated at baseline. Any additional non-active psoriatic lesions (i.e. lesions not present at baseline that have been cleared or almost cleared by rescue treatment during a

relapse) should be treated with maintenance IP as well. Maintenance IP should be applied 3 or 4 days apart. The choice of the application days will be left to subjects' preference, and these days will be fixed throughout the trial (e.g., Thursday and Sunday); this needs to be settled at Visit 2. Subjects will be assessed by the investigator at the trial site every 4 weeks from Visit 2 to Visit 15. Furthermore, depending on when relapse occurs in relation to the regular 4-week visits (also referred to as 'scheduled' visits), additional (unscheduled) visits may be needed (outlined below).

All regular 4-week (scheduled) visits between or after an unscheduled visit or relapse follow-up visit should be performed.

Based on these rules, there are the following options:

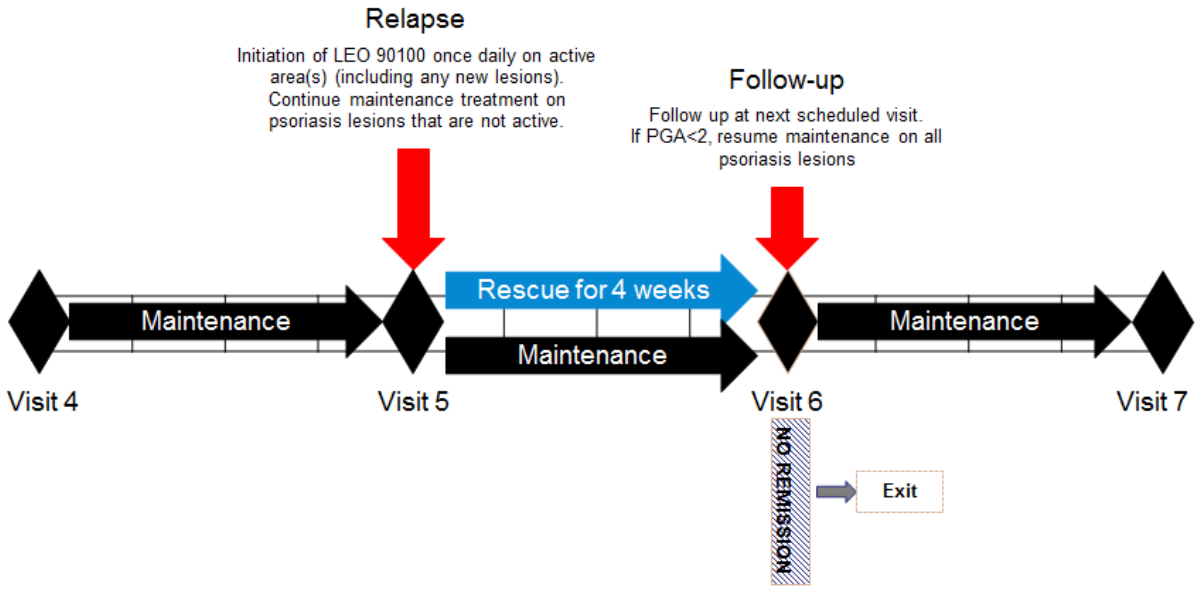
6.1.4.1 Relapse at a regular 4-week (scheduled) visit

In case a relapse of psoriasis (defined as PGA of at least 'mild') is observed by the investigator at a regular monthly visit, the subject will be provided with rescue IP and instructed to apply it on the affected areas on trunk and limbs once daily for 4 weeks (all active psoriatic lesions including any new areas that become active during this 4-week treatment period).

Twice weekly maintenance treatment will continue unchanged on areas that are not active.

The subject will return to the trial site 4 weeks later to attend the regular monthly visit, where, if the subject is 'clear' or 'almost clear' according to PGA, maintenance treatment will be resumed on those areas. If the PGA of 'clear' or 'almost clear' is not achieved after 4 weeks of rescue treatment, the subject will exit the trial. For illustration, see Figure 2 below.

Figure 2 Relapse at a regular 4-week (scheduled) visit



6.1.4.2 Relapse between regular 4-week (scheduled) visits – more than one week prior to the next regular visit

If, in the opinion of the subject, a relapse of psoriasis occurs between regular visits when there is ***more* than one week (7 days) to the next planned visit**, the subject will contact the trial site to be assessed by the investigator at an unscheduled visit.

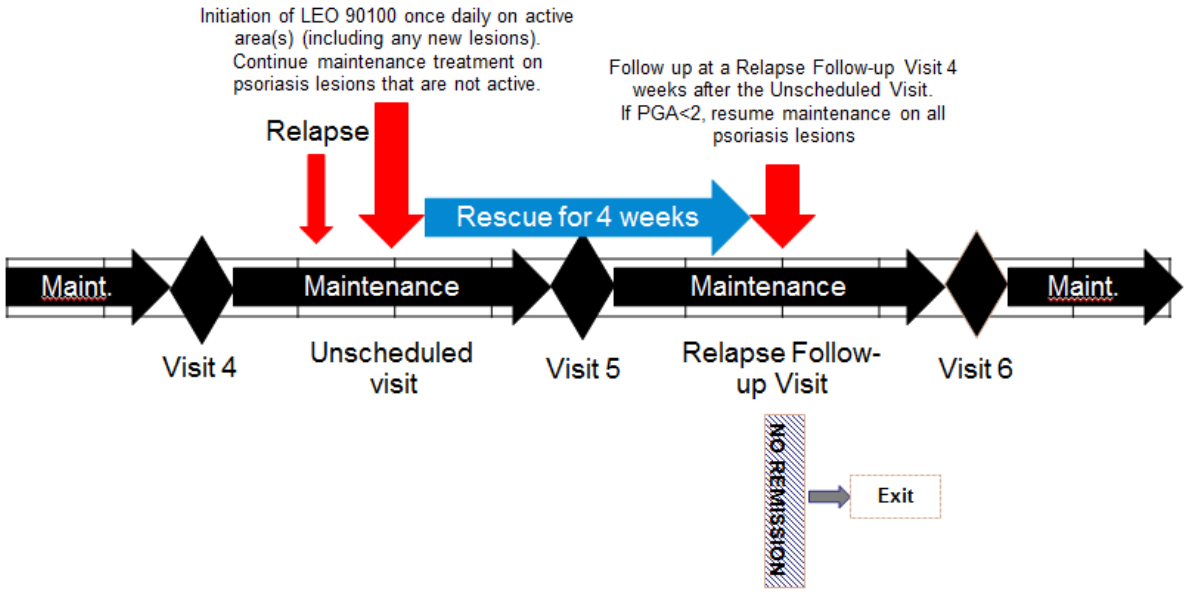
If relapse is confirmed by the investigator, the subject will be provided with rescue IP and instructed to apply it once daily for 4 weeks on any active psoriatic lesions on trunk and limbs during this time.

Twice weekly maintenance treatment will continue unchanged on areas that have not relapsed.

The subject will be examined at the next regular 4-week visit, but even if 'clear'/'almost clear' at the regular visit, rescue treatment will continue. A relapse follow-up visit will take place at a relapse follow-up visit 4 weeks after the unscheduled visit where relapse treatment was initiated. If the subject is 'clear' or 'almost clear' according to PGA at this relapse follow-up visit, maintenance treatment on those areas will be resumed and the subject will follow the planned visit schedule.

If the subject is not 'clear'or 'almost clear' according to PGA after 4 weeks of relapse treatment, they will exit the trial. For illustration, see Figure 3 below.

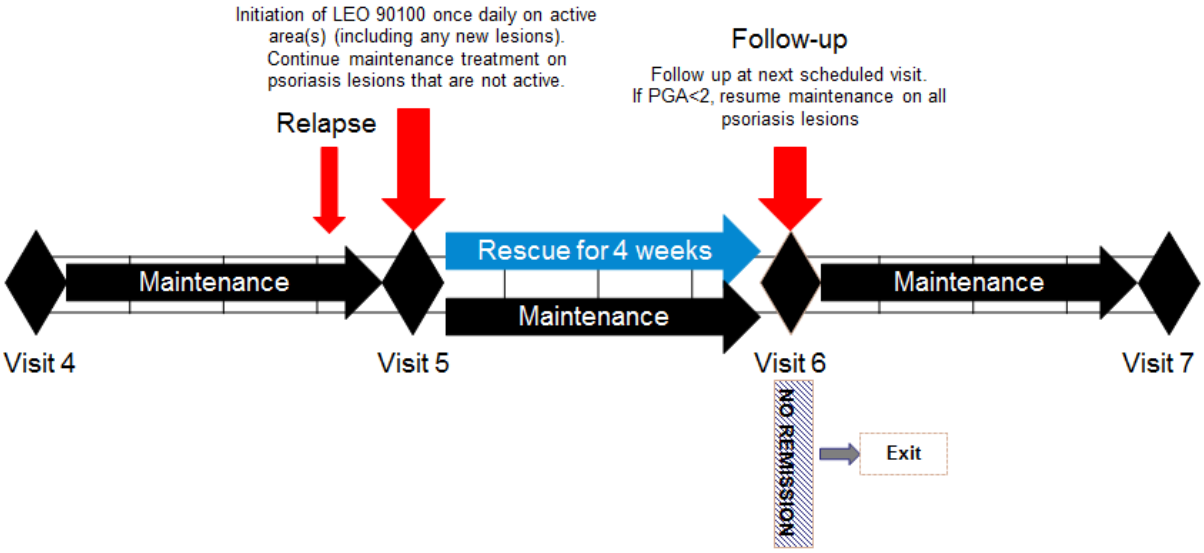
Figure 3 Relapse between regular 4-week (scheduled) visits – <u>more than one week prior to the next regular visit</u>



6.1.4.3 Relapse between regular 4 week (scheduled) visits – <u>less than one week to the next regular visit</u>

If a relapse/exacerbation of psoriasis occurs **<u>within one week (7 days) prior to the next scheduled visit</u>**, the subject should attend the next scheduled visit and the procedure described in section 6.1.4.1 should be followed. For illustration, see Figure 4 below.

Figure 4 Relapse between regular 4 week (scheduled) visits – <u>less than one week to the next regular visit</u>



<u>Trial visits (initial open-label treatment phase and maintenance phase)</u>

The total trial duration will be up to 64 weeks (including 8 weeks follow-up) and will include at least 15 regular visits.

All post-randomisation visits (Visits 3 to 15) should be performed within ± 4 days of the scheduled time relative to Visit 2; if the visit is performed outside of the visit window, the investigator should record the reason in the subject's medical record. The same visit window (± 4 days) is applicable for the follow-up of any unscheduled visits due to relapse.

The maintenance IP will be dispensed at each regular visit (from Visit 1 to Visit 14) and used maintenance IP will be collected at the next regular visit (from Visit 2 to Visit 15). Rescue IP will either be dispensed at a regular visit and collected at the next regular visit, or be dispensed at an unscheduled visit and collected at a relapse follow-up visit 4 weeks later, as applicable. The number of cans to be dispensed depending on the different trial phases is specified in section 10.4. Subjects should not discontinue treatment themselves between the trial visits. This applies to both maintenance treatment and rescue treatment following relapse.

The DLQI and EQ-5D-5L-PSO questionnaires will be completed at each visit to the site.

In addition, the subjects will be asked to complete the WPAI:PSO at baseline (Visit 1), at randomisation (Visit 2/Week 4), after approximately 6 months (Visit 8/Week 28) and at the end of treatment (Visit 15/Week 56).

At baseline (Visit 1), subjects will be instructed on how to capture psoriasis symptoms in the eDiary (e.g. erythema, scaliness, itching, etc…) using the PSI.

At home, subjects will complete the PSI daily during the open-label treatment phase (starting at Visit 1), then weekly during the first 28 weeks of the maintenance phase (Weeks 4 to 28) and the 2 last weeks of the maintenance phase (Week 54 to 56 - only applicable for completers).

The eDiary will also be used to record adherence to the once daily treatment regimen during the initial open-label treatment phase as well as the twice weekly and once-daily treatment regimens during the maintenance phase and relapse.

6.1.5 Follow-up Phase

There are three types of follow-up visits, here listed in chronological order:

Follow-up Visit 1 (FU1):

A follow up visit 1 is only relevant for subjects with an ongoing AE at end of treatment. A follow-up visit/contact (FU1) should be conducted 14 (± 2) days after the last on-treatment visit (Visit 15/Early Withdrawal), unless the final outcome of the event, as defined below, has been determined before then.

This follow-up visit/contact (FU1) will take place only if:

1. there is an on-going SAE at the last on-treatment visit.
2. there is an on-going non-serious AE at the last on-treatment visit which is classified as possibly or probably related to the IPs
3. the albumin-corrected serum calcium is above the reference range at the last on-treatment visit
4. the calcium:creatinine ratio is above the reference range and clinically significant at the last on-treatment visit

Where the (sub)investigator considers it appropriate, the Follow-up Visit may be performed as a telephone contact. If a subject also is elegible for a follow up visit 2 (FU2), the follow-up on the ongoing AE can wait until FU2 (see below).

Follow-up Visit 2 (FU2):

For subjects undergoing the adrenocorticotropic hormone (ACTH) challenge test, a follow-up visit (Visit FU2) will take place 28 days after the ACTH challenge test performed at the end of treatment (Visit 15/Early Withdrawal) if the end of treatment test shows a serum cortisol concentration ≤18 mcg/dl at both 30 minutes and 60 minutes after ACTH challenge (39, 40).

If the results of the ACTH challenge test at Visit FU2 continue to show a serum cortisol concentration ≤18mcg/dl at both 30 minutes and 60 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 or at 60 minutes after the ACTH-challenge, or at both time-points).

Refer to Section 8.12.1 for further details on the ACTH challenge test.

Follow-up visits should be performed within ±4 days of the scheduled time; if they are outside this window, the (sub)investigator should record the reason in the subject's medical record but LEO do not need to be notified.

Follow-up Visit 3 (FU3):

All subjects should be followed up for events of rebound for 8 weeks after last application of IP. The different scenarios are outlined below:

- Subjects who do not use rescue medication at Visit 15 will have a final contact (FU3) 8 weeks after Visit 15. Relapses confirmed at Visit 15 will be treated at the investigator's discretion; treatment with Enstilar® or IP is not allowed.
- Subjects who have completed 4 weeks of rescue treatment at Visit 15 (that is, Visit 15 is a relapse follow-up visit, see section 6.1.4.1) will have a final contact (FU3) 8 weeks after Visit 15.
- For subjects who use rescue medication at Visit 15 (that is, rescue medication was dispensed at an unscheduled visit after Visit 14 [see section 6.1.4.2]), the 8-week follow-up period will start after completion of the 4-week rescue treatment regimen (that is, at the relapse follow-up visit).

- Subjects who withdraw early from the trial, including subjects who leave the trial after the initial 4 weeks open-label treatment, will also have a follow-up visit (FU3) 8 weeks after their last IP application.

Subjects who experience rebound during the follow-up period prior to the FU3 visit will contact the site as soon as possible for an unscheduled follow-up visit (see below).

If the subject has not experienced a worsening of their psoriasis during the 8-week follow-up period, the FU3 contact may be conducted as a telephone contact, at the discretion of the investigator. If rebound is confirmed at the FU3 visit, the subject will be followed up for 14 days or until resolution (whichever occurs first). If the rebound is considered an SAE, the event 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 (see section 9.5).

Rebound events in the follow-up period will be reported as (S)AEs in accordance with sections 9.2 and 9.4.1. See section 9.5 for the follow-up of related AEs during and after the trial.

Unscheduled follow-up visit
At the last treatment visit (Visit 15/Early Withdrawal), subjects should be instructed to contact the site if they experience a worsening of their psoriasis within the following 8 weeks to schedule a follow-up visit ('unscheduled follow-up'). The unscheduled follow-up visit should take place no more than 7 days after the initial contact.

If a relapse or rebound is confirmed at an unscheduled follow-up visit, the subject will be treated at investigator's discretion according to clinical practice. Note that relapse or rebound should not be treated with trial medication or Enstilar® during the follow-up period. The subject may come back to the trial site for another unscheduled follow-up visit, at the investigator's discretion. The subject will continue in the follow-up phase until the FU3 visit. If the subject experiences another worsening of their psoriasis within the 8-weeks follow-up period, they will contact the site again for a new unscheduled follow-up visit.

6.2 Sample Size

A total of 380 subjects should be randomised in the trial in order to have power for the primary maintenance treatment objective. In order to achieve 380 randomised subjects it is estimated that 832 subjects should be included in the trial.

The total number of subjects treated in the trial should also be sufficient to comply with ICH E1 regarding long-term safety. The aim is to achieve at least 300 subjects with 26 weeks of exposure and at least 100 subjects with 52 weeks of exposure.

For the HPA axis test, the aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure.

The total number of randomised subjects can exceed 380 in order to achieve a sufficient number of subjects for long-term evaluation of safety and HPA testing.

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

6.3 Randomisation

Subjects will be randomised in a 1:1 ratio to receive LEO 90100 or vehicle twice weekly during the maintenance phase. Randomisation will be stratified by trial site, HPA axis testing, and by baseline disease severity (mild, moderate, severe).

6.4 Blinding

During the open-label treatment phases (initial and relapse treatment), all subjects will receive LEO 90100.

During the maintenance phase, this trial is double-blind. Therefore, the packaging and labelling of the IPs must contain no evidence of their identity. It is not considered possible to differentiate between the IPs solely by sensory evaluation. No effects of the IPs which would reveal the identity of the individual treatment allocations are expected. Consequently, it is expected that the subjects and the site staff remain unaware of the individual treatment assignment during the conduct of the clinical trial.

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" [cf. 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

1. Signed and dated informed consent obtained prior to any trial related activities (including washout period)
2. Age 18 years or above
3. A clinical diagnosis of psoriasis vulgaris for at least 6 months involving the trunk and/or limbs, amenable to treatment with maximum of 100 g of trial medication per week
4. Psoriasis vulgaris on the trunk and/or limbs (excluding psoriasis on the genitals and skin folds) involving 2-30% of the body surface area (BSA)
5. A Physician's Global Assessment of disease severity (PGA) of at least 'mild' on trunk and limbs at Visit 1
6. A m-PASI score of at least 2 at Visit 1
7. A target lesion/target location of at least 3 cm at its longest axis located on the body (i.e., not on the scalp, face or intertriginous areas), scoring at least 1 ('mild') for each of redness, thickness and scaliness, and at least 4 in total by the Investigator's Assessment of Severity of the Target Lesion/Location
8. Females of child-bearing potential must have a negative urine pregnancy test at Visit 1
9. Females of child-bearing potential must agree to use a highly effective method of birth control during the trial*
10. Able to communicate with the investigator and understand and comply with the requirements of the trial

*A highly effective method of birth control is defined as one which results in a low failure rate (less than 1% per year) such as implants, injectables, combined oral contraceptives, some intra-uterine devices, sexual abstinence or vasectomised partner. The subjects must have used the contraceptive method continuously for at least 1 month prior to the pregnancy test, and must continue using the contraceptive method for at least 1 week after the last application of trial medication. A female is defined as not of child-bearing potential if she is postmenopausal (12 months with no menses without an alternative medical cause), or surgically sterile (hysterectomy or bilateral overiectomy).

Additional inclusion criteria for subjects undergoing HPA axis test (assigned sites only):

11. Signed and dated informed consent obtained for having ACTH challenge tests performed
12. An extent of psoriasis vulgaris on trunk and/or limbs of disease severity (PGA) of at least 'moderate' affecting between 10 and 30% of the body surface area (BSA) excluding psoriatic lesions of genitals and skin folds at Visit 1
13. At Visit 1, a normal HPA axis function including a serum cortisol concentration above 5 mcg/dl before ACTH-challenge and above 18 mcg/dl 30 minutes after ACTH-challenge.

7.3 Exclusion Criteria

1. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time periods prior to Visit 1:
    - etanercept – within 4 weeks prior to Visit 1
    - adalimumab, infliximab – within 8 weeks prior to Visit 1
    - ustekinumab – within 16 weeks prior to Visit 1
    - secukinumab – within 12 weeks prior to Visit 1
    - other products – within 4 weeks/5 half-lives prior to Visit 1 (whichever is longer)
2. Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (e.g. corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants) within 4 weeks prior to Visit 1
3. Systemic treatment with apremilast within 4 weeks prior to Visit 1
4. Subjects who have received treatment with any non-marketed drug substance (i.e. a drug which has not yet been made available for clinical use following registration) within 4 weeks/5 half-lives (whichever is longer) prior to Visit 1
5. Psoralen combined with Ultraviolet A (PUVA) therapy within 4 weeks prior to Visit 1
6. Ultraviolet B (UVB) therapy within 2 weeks prior to Visit 1
7. Topical anti-psoriatic treatment on the trunk and/or limbs (except for emollients) within 2 weeks prior to Visit 1
8. Topical treatment on the face, scalp and skin folds with corticosteroids, or vitamin D analogues within 2 weeks prior to Visit 1

9. Severe and/or extensive scalp psoriasis which, in the opinion of the investigator, requires treatment with potent or super-potent corticosteroids which will be prohibited during the trial
10. Pre-existing overt atrophy or teleangiectasia in treatment areas
11. Planned initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (e.g. beta blockers, antimalarial drugs, lithium, ACE inhibitors) during the trial
12. Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis
13. Subjects with any of the following conditions present on the treatment area: 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, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichtyosis, ulcers and wounds
14. Other inflammatory skin disorders (e.g. seborrhoeic dermatitis or contact dermatitis) on the treatment area that may confound the evaluation of psoriasis
15. Planned excessive exposure of area(s) to be treated with trial medication to either natural or artificial sunlight (including tanning booths, sun lamps etc.) during the trial
16. Known or suspected disorders of calcium metabolism associated with hypercalcaemia
17. Known or suspected hypersensitivity to component(s) of investigational products
18. Current participation in any other interventional clinical trial
19. Previously screened in this trial
20. In the opinion of the (sub)investigator, the subject is unlikely to comply with the clinical trial protocol (e.g. due to alcoholism, drug addiction or psychotic state)
21. Females who are pregnant, wishing to become pregnant during the trial or are breastfeeding
22. Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a contract research organization (CRO) involved in the trial
23. Subjects who are institutionalized by court order or by local authority.

Additional exclusion criteria for subjects undergoing HPA axis test (assigned sites only):

24. A history of allergic asthma, serious allergy or serious allergic skin rash

25. Known or suspected hypersensitivity to component(s) of CORTROSYN® (including cosyntropin/tetracosactide) (in the US) / Synacthen® (including tetracosactide) (in Europe)
26. The use of inhaled corticosteroids in the 4 weeks prior to Visit 1 or during the trial
27. Systemic corticosteroid treatment in the 12 weeks prior to Visit 1 or during the trial
28. Enzymatic inductors (e.g., barbiturates, phenytoin, rifampicin) within 4 weeks prior to Visit 1 or during the trial
29. Systemic or topical cytochrome P450 inhibitors (e.g., ketoconazole, itraconazole, metronidazole) within 4 weeks prior to Visit 1 or during the trial. Topical ketoconazole within 2 weeks prior to Visit 1
30. Hypoglycemic sulfonamides within 4 weeks prior to Visit 1 or during the trial
31. Antidepressive medications within 4 weeks prior to Visit 1 or during the trial. Oestrogen therapy (including contraceptives), antidepressant medications and any other medication known to affect cortisol levels or HPA axis integrity within 4 weeks prior to baseline
32. Not following nocturnal sleep patterns
33. Any of the following conditions, whether known or suspected:
    - depression and endocrine disorders (e.g. Cushing's disease, Addison's disease, diabetes mellitus) known to affect cortisol levels or HPA axis integrity
    - cardiac disorders associated with abnormal QT intervals or rhythm disturbances including clinically significant bradycardia or tachycardia
    - severe renal insufficiency
    - severe hepatic disorders.

7.4 Screening failures

For screening failures the following must be collected: reason for not continuing in the trial, SAEs and AEs. Follow-up of SAEs must be carried out according to section 9.5.

7.5 Subject Enrolment Log

All subjects screened for this trial will be recorded on an enrolment log. The log will record whether subjects were enrolled or not. If a subject is not enrolled, the main reason for non-

enrolment will be listed. The log will be prepared according to local regulations regarding personal data protection.

Additionally, all subjects that fail screening will be accounted for in the electronic case report form (eCRF). These subjects will be identified by a subject ID and date or year of birth.

7.6 Subject Identification List

The (sub)investigator must maintain a list of all subjects entering the open-label phase at the trial site including each subject's identity, date of enrolment and corresponding subject 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.

At screening visit, 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.

The subject ID is distinct from the randomisation code number.

7.7 Subject card

At screening, subjects will be provided with a card stating that they are participating in a trial and giving contact address(es) and telephone number(s) of relevant trial site staff.

7.8 Restrictions during Trial

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

7.8.1 Restrictions prior to the start of treatment (Visit 1)

The washout phase is up to 4 weeks (28 days). Subjects who are being treated with medications requiring more than 4 weeks washout will not be eligible for the trial.

However, subjects might be eligible if they had a treatment-free period prior to entering the trial (i.e. having signed the Informed Consent).

Note: the treatment-free period prior to entering the trial is not a trial related procedure and accordingly not part of the trial defined wash-out phase. The earliest possible wash-out start date to record in the eCRF is the day the subject entered the trial (i.e. having signed the Informed Consent).

To account for an adequate treatment-free period, the date of last use of the excluded medication will be recorded in the eCRF.

Treatments requiring washout

Treatments requiring washout before Visit 1 are listed in Table 1 (all subjects) and Table 2 (subjects performing HPA axis test) below, together with the required individual washout periods.

7.8.2 During the Trial Treatment Phase (open-label treatment phase and maintenance phase)

Treatments which cannot be used during the treatment period (Visit 1 to Visit 15) are listed in Table 1 (applicable to all subjects).

Table 1: 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 and not marketed), with a possible effect on psoriasis vulgaris	Not applicable	• Etanercept: within 4 weeks prior to Visit 1 • Adalimumab, infliximab: within 8 weeks prior to Visit 1 • Ustekinumab: within 16 weeks prior to Visit 1 • Secukinumab: within 12 weeks prior to Visit 1 • Other products: within 4 weeks/5 half-lives prior to Visit 1 (whichever is longer) and any time during the trial treatment phase
Systemic treatment with therapies other than biologicals, with a possible effect on psoriasis vulgaris (e.g., corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants)	Not applicable	Within 4 weeks prior to Visit 1 and any time during the trial treatment phase
Systemic treatment with apremilast	Not applicable	Within 4 weeks prior to Visit 1 and any time during the trial treatment phase
Use of non-marketed/other IPs	Body and scalp	Within 4 weeks or 5 half-lives (whichever is longer) prior to visit 1 and any time during the trial treatment phase
Psoralen combined with UVA therapy (PUVA)	Body and scalp	Within 4 weeks prior to Visit 1 and any time during the trial treatment phase
UVB therapy	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	Body and	Within 2 weeks prior to visit 1 and any time

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
including corticosteroids (except for emollients, non-steroid medicated shampoos and low potency corticosteroids on sensitive areas), see Table 3	Scalp	during the trial treatment phase. On areas treated with IP, emollients should not be used on days where IP is being applied.
Initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (e.g. beta-blockers, lithium, anti-malaria drugs, ACE inhibitors)	Not applicable	Any time during the trial treatment phase
Vitamin D supplements > 400 IU/day, (note: stable dose of vitamin D supplements ≤ 400 IU/day is permitted)	Not applicable	Any time during the trial treatment phase
Excessive exposure of treated areas to either natural or artificial sunlight that may affect psoriasis vulgaris. (i.e., normal lifestyle outdoor activities are permitted but deliberate exposure to sunlight or artificial ultraviolet light like tanning booths should be avoided)	Body and Scalp	Any time during the trial treatment phase

For subjects performing HPA axis test, additional treatments requiring washout before Visit 1 and prohibited during the trial are listed in Table 2 below, with the required individual washout periods:

Table 2: Prohibited Medication including Non-Drug Therapies and Procedures (for subjects performing HPA axis test)

Prohibited Medication including Non-Drug Therapies and Procedures	Location	Exclusion Period Restrictions
Systemic treatment with corticosteroids	Not applicable	Within 12 weeks prior to V1 and any time during the trial treatment phase
Inhaled corticosteroids	Not applicable	Within 4 weeks prior to V1 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	Not applicable	Within 4 weeks prior to V1 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	Body and Scalp	Within 4 weeks prior to V1 and any time during the trial treatment phase
Topical ketoconazole	Body and Scalp	Within 2 weeks prior to V1 and any time during the trial treatment phase

For all subjects, a stable concomitant treatment regimen with other drugs that have a potential effect on psoriasis (e.g. beta-blockers, anti-malarials and ACE inhibitors) is allowed during the trial.

Inhaled steroids are allowed during the trial (except during the last 4 weeks prior to ACTH-challenge for subjects participating in the HPA axis part).

Bath oils and moisturising soaps are allowed during the trial.

Sunscreens are allowed but should not be applied at the same time as the trial medication (an interval of at least 1 hour is recommended between applications).

Any skin conditions other than psoriasis may be treated with topical therapy as appropriate provided the treatment does not affect the assessment, treatment or severity of psoriasis. The topical therapy should be applied only on the target area(s) of the skin condition and not on the area(s) of psoriasis.

Concomitant anti-psoriatic treatments allowed during the trial is listed in Table 3:

Table 3: Permitted concomitant anti-psoriatic treatment

Location	Permitted concomitant anti-psoriatic treatment
Scalp	Non-medicated and medicated shampoos/products except those that contain corticosteroids or vitamin D analogues (e.g., tar, salicylic acid, tazaroten, anthraline) are allowed. Topical use of mild corticosteroids (class 6-7) is allowed, but should be for short term use and be minimized to the largest possible extent.
Trunk/limbs	Bath oils and moisturizing soaps are allowed. Unlimited use of emollients (except within 6 hours of clinic visits) is allowed. Emollients used should not contain alpha-hydroxy acids, beta-hydroxy acids or acetylic acid; Emollients containing urea acid (≤ 5%) are allowed.
Face and sensitive areas	Any topical treatments other than class 1-5 corticosteroids or Vitamin D analogues (calcipotriol, calcitriol or tacalcitol) are allowed (e.g. topical calciuneurin inhibitors). Topical use of mild corticosteroids (class 6-7) is allowed, but should be for short term use and be minimized to the largest possible extent. 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*	

7.8.3 Follow-up period

During the follow-up period, subjects who require a repeat ACTH-challenge test at FU2 (Section 6.1.5) 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.

Note that treatment with Enstilar® or IP is not allowed during the follow-up period (Section 6.1.5).

7.9 Discontinuation

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

1. *Screening failure*
2. *Lack of efficacy:* The (sub)investigator is free to withdraw the subject at any time based on a medical judgement.

3. *Adverse event (please specify):* Any adverse event (AE) that the (sub)investigator considers unacceptable.
4. *Withdrawal by subject:* Subjects are free to withdraw from the clinical trial at any time and for any reason.
5. *Lost to follow-up*
6. *Death*
7. *Other (please specify):* Other reasons than stated above which require the subject to (be) withdraw(n) should be specified.

Subjects **must** be withdrawn from the trial for any of the following reasons:

8. *Subjects who do not achieve treatment success (PGA score of 'clear' or 'almost clear' with at least a 2-grade improvement from baseline) after initial 4-week treatment*
9. *Subjects who are not scored as 'clear' or 'almost clear' after 4-week treatment of relapse*

If adverse event or other is selected, a specification must be supplied.

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.

The final efficacy assessment (at the correct scheduled time) should be attempted to be completed for all subjects. Such deviation(s) from the (Consolidated) Clinical Trial Protocol must be reported to LEO Pharma A/S (and Independent Ethics Committee (IEC)/Institutional Review Board (IRB), as appropriate) and recorded in the Clinical Study Report.

Reason(s) for discontinuation from trial will be recorded in the eCRF. Subjects withdrawn will not be substituted.

8 Trial Schedule and Assessments

8.1 Schedule of Trial Procedures

The schedule of trial procedures is shown in Table 4.

Table 4: Schedule of Trial Procedures

	Screening	Open-label phase 4 wks	Maintenance phase					Follow-up phase			
	SV[1)]	Visit 1[2)] Baseline	Visit 2 Randomi-sation	V3 to V14	V15	UNS/ Relapse FU visit[17)]	Early Withdrawal	FU1[18,20)]	FU2[19,20)]	FU3[21)]	UNS FU[22)]
Frequency		Every 4 weeks (from V1 to V15) relative to V2								8 weeks after V15/EW	As needed
Visit window		±4 days (from V1 to V15)				No more than 7 days after subject calls		±2 days	±4 days	±4 days	≤ 7 days after call
Informed consent[3)]	X										
Informed consent for biomarkers[3)]	X										
Informed consent for ACTH challenge tests[3)]	X										
Informed consent for photographs[3)]	X										
Inclusion/Exclusion criteria	X	X									
Demographics	X										
Fitzpatrick Skin type	X										
Height and weight	X										
Vital signs (BP, pulse)		X	X		X		X				
Physical examination	X		X[4)]		X		X			X[25)]	
Medical history/ locations of psoriasis	X										

	Screening	Open-label phase 4 wks	Maintenance phase					Follow-up phase			
	SV[1)]	Visit 1[2)] Baseline	Visit 2 Randomi-sation	V3 to V14	V15	UNS/ Relapse FU visit[17)]	Early Withdrawal	FU1[18,20)]	FU2[19,20)]	FU3[21)]	UNS FU[22)]
Frequency		Every 4 weeks (from V1 to V15) relative to V2								8 weeks after V15/EW	As needed
Visit window		±4 days (from V1 to V15)				No more than 7 days after subject calls		±2 days	±4 days	±4 days	≤ 7 days after call
Previous anti-psoriatic therapy	X										
Concomitant medication and procedures	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[5)]		X	X	X	X		X				
Randomisation			X								
Adverse Event[6)]	X	X	X	X	X	X	X	X	X	X	X
Laboratory: Biochemistry		X	X[7)]		X[8)]		X[8)]	X			
Laboratory: 25-OH Vitamin D		X									
Urinalysis		X	X[7)]		X[8)]		X[8)]	X			
Laboratory: ACTH challenge test (assigned sites only)[9)]		X	X	X[10)]	X		X[24)]		X[23)]		
Sampling for biomarkers[11)]		X		X[10)]	X[12)]		X[12)]				
Subject's Global Assessment of disease severity		X	X	X	X	X	X				

	Screening	Open-label phase 4 wks	Maintenance phase					Follow-up phase			
	SV[1)]	Visit 1[2)] Baseline	Visit 2 Randomi-sation	V3 to V14	V15	UNS/ Relapse FU visit[17)]	Early Withdrawal	FU1[18,20)]	FU2[19,20)]	FU3[21)]	UNS FU[22)]
Frequency		Every 4 weeks (from V1 to V15) relative to V2								8 weeks after V15/EW	As needed
Visit window		±4 days (from V1 to V15)				No more than 7 days after subject calls		±2 days	±4 days	±4 days	≤ 7 days after call
Subject - Local safety and Tolerability		X	X	X	X	X	X				
Physician's Global Assessment of disease severity	X	X	X	X	X	X	X			X[25)]	X
Selection of the target lesion/location		X									
Investigator's Assessment of the Severity of the target lesion/location		X	X	X	X	X	X			X[25)]	X
Photographs of the target lesion/loc [11,13)]		X	X	X	X	X	X				
Local safety and Tolerability – Physician		X	X	X	X	X	X			X[25)]	X
m-PASI		X	X	X	X	X	X			X[25)]	X
BSA		X	X	X	X	X	X			X[25)]	X
DLQI		X	X	X	X	X	X				
EQ-5D-5L		X	X	X	X	X	X				
WPAI:PSO		X	X	X[10)]	X		X				

	Screening	Open-label phase 4 wks	Maintenance phase					Follow-up phase			
	SV[1)]	Visit 1[2)] Baseline	Visit 2 Randomi-sation	V3 to V14	V15	UNS/ Relapse FU visit[17)]	Early Withdrawal	FU1[18,20)]	FU2[19,20)]	FU3[21)]	UNS FU[22)]
Frequency		Every 4 weeks (from V1 to V15) relative to V2								8 weeks after V15/EW	As needed
Visit window		±4 days (from V1 to V15)				No more than 7 days after subject calls		±2 days	±4 days	±4 days	≤ 7 days after call
Psoriasis symptom inventory		Daily during the open-label phase Weekly during the first 28 weeks of the maintenance phase and the 2 last weeks of the maintenance phase (for completers only)									
Compliance check[14)]-eDiary		Daily during the open-label phase Weekly during the maintenance phase (including relapse treatment)									
Subject treatment instructions		X	X			X					
Dispensing of IP		X	X	X		X[15)]					
Return of IP			X	X	X	X[16)]	X				
Drug compliance Form			X	X	X	X	X				
End of Trial Form							X			X	

1) A washout period of up to 4 weeks must be completed if the subject is treated or has recently been treated with anti-psoriatic treatments or other relevant medication, as defined by the exclusion criteria.

2) SV and Visit 1 can be performed at the same time for subjects who do not need a washout period.

3) Informed consent should be signed both by subject and (sub)investigator (medically qualified) before any trial related procedures are carried out. For subjects requiring a washout period, informed consent should be completed prior to washout.

4) Physical Examination at Visit 2 is required if the subject will not be randomised

5) Only applicable for women of child-bearing potential.

6) AEs will be collected from the date of signing the informed consent form i.e. during the washout period.

7) If albumin-corrected serum calcium is above the normal range, or if calcium:creatinine ratio is above the normal range and judged as clinically significant at this visit, sampling should be repeated at the following visit (Visit 3 or FU1)

8) If albumin-corrected serum calcium is above the normal range, or if calcium:creatinine ratio is above the normal range and judged as clinically significant at this visit, sampling should be repeated at a follow-up visit

9) Applicable only to subjects performing HPA axis assessments. ACTH challenge test should be performed at 8.00 a.m. ±30 min after checking vital signs and collecting blood and urine samples.

10) At Visit 8 (Week 28) only.

11) Only for subjects who consented for this procedure.

12) Or earlier in case of early withdrawal fors subjects who have completed at least 40 weeks of the trial from baseline.

13) At designated sites.

14) Treatment compliance will be recorded by the subject in an eDiary.

15) In case of relapse, LEO 90100 will be dispensed at any unscheduled visit during the maintenance phase.

16) Subjects will have to return LEO 90100 dispensed during any unscheduled visit (UNS) at the following relapse follow-up visit (Relapse FU) or at the next regular 4-week visit.

17) Unscheduled visit (UNS) or relapse follow-up visit (Relapse FU) to be performed in case a relapse of psoriasis occurs (see figures section 6.1.4).

18) FU1 visit should only be performed if required, e.g. in case a non-serious AE is classified as possibly or probably related to the trial treatment or an SAE is on-going at the last on-treatment visit. Where the (sub)investigator considers it appropriate, the FU1 visit may be performed as a telephone contact. To be performed 2 weeks after the last on-treatment visit.

19) FU2 visit only applicable for subjects for whom the ACTH challenge test at end of treatment shows a serum cortisol concentration ≤18 mcg/dl at both 30 minutes and 60 minutes after ACTH-challenge. The FU2 visit will be performed 4 weeks after the last-on treatment visit.

20) If both FU1 and FU2 are applicable (only applicable for subjects performing HPA axis assessments), only FU2 (4 weeks after the last on-treatment visit) will be performed. All assessments applicable at FU1 will be done at FU2.

21) Subjects will be followed up for 8 weeks after V15/EW for relapse/rebound evaluation. If the subject has not experienced a worsening of their psoriasis during the 8 week follow-up period, the FU3 contact may be conducted as a telephone contact, at the discretion of the investigator.

22) Subjects who experience a worsening of their psoriasis during the follow-up phase prior to the FU3 visit will contact the site as soon as possible for an unscheduled follow-up visit (section 6.1.5).

23) Subjects with a serum cortisol concentration ≤18mcg/dl at both 30 minutes and 60 minutes after ACTH challenge at FU2 will be followed up until the adrenal suppression resolves. Further ACTH challenge tests must be captured in the UNS FU page in the eCRF.

24) If the subject withdraws prior to completing the initial open-label treatment phase, the ACTH-challenge test should not be performed.

25) Only required if last FU3 is performed at the trial site.

EW, early withdrawal; FU, follow-up; IP, investigational product; SV, screening visit; UNS, unscheduled visit; UNS FU, unscheduled follow-up visit; V, visit.

8.2 Demographics

Subject's demographic details (date of birth or month/year only and self-reported age (depending on participating countries), sex, race, ethnic origin (ethnicity)) must be recorded.

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).

8.3 Fitzpatrick Skin Type

The skin type of the subjects will be recorded using the classification specified in Table 5.

Table 5: Fitzpatrick Skin Classification

Fitzpatrick 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

8.4 Height and Weight

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

8.5 Vital Signs

Vital signs will include blood pressure (systolic and diastolic recorded in mmHg) and heart rate (beats per minute). Heart rate and blood pressure will be measured after approximately 5 minutes resting.

8.6 Physical Examination

An abbreviated physical examination including general appearance, regional lymph nodes and dermatologic examination of the skin must be performed at visits indicated in section 8.1.

Abnormal, clinical significant findings at the screening visit should be recorded as diagnoses in the Concomitant Medication page if medication is currently being taken for the condition.

If not, it will be documented as medical history in the eCRF. From Visit 1, any clinically significant deterioration of a pre-existing condition as well as any new illness, symptom or clinically significant sign will be reported as an AE in accordance with section 9.2.

8.7 Medical History

Relevant medical history and concurrent diagnoses will be recorded based on subject interview. The duration of psoriasis will be recorded (to the nearest whole year).

Locations of Psoriasis

The presence of psoriasis lesions on the trunk and limbs that constitute the treatment areas (upper leg, knee, lower leg including foot, upper arm, elbow, forearm including hand, chest, abdomen, neck, upper back, lower back) will be recorded.

The presence of psoriasis affecting regions of the body not considered to be part of the treatment area (i.e. face, scalp, skin folds, genitals, palms, soles, and nails) will also be recorded.

Previous anti-psoriatic therapy

All previous anti-psoriatic treatment (systemic and topical medications and light therapy) used by the subject to treat their psoriasis vulgaris over the past 2 years will be recorded by pre-defined categories. Latest treatment (within 4 months) prior to screening will also be recorded.

8.8 Concomitant Medication and Procedures

Concomitant medication is defined as any medication used by a subject during the clinical trial apart from the IPs. Use of concomitant treatment must be recorded in the subject's medical record and the eCRF (e.g. treatment/drug name, route of administration, total daily dose, indication and dates of start and stop).

For topical treatment, it must be recorded if the concomitant treatment is within 2 cm (appr. 1 inch) of the areas treated with the IP.

Any concomitant medication and procedure must be recorded at visits indicated in Section 8.1. Details should include body location, diagnosis, start/stop date and if the procedure is inside the treatment areas.

8.9 Pregnancy Test

A urine pregnancy test will be performed at the trial site at Visit 1, prior to randomisation (Visit 2), and at all the subsequent visits including the last on-treatment visit (or earlier in case of premature withdrawal). The test will only be performed in female subjects of child-bearing potential. The test kits will be provided by the Central Laboratory.

8.10 Adverse Events

AEs must be assessed and recorded as specified in section 9.

8.11 Other Safety Assessments

All physician's dermatologic assessments of the treatment area must be performed by a dermatologist, certified physician's assistant, advanced registered nurse practitioner or general practitioner experienced in treating psoriasis vulgaris. The same person should attempt to perform all dermatologic examinations of each individual subject.

The following assessment must be performed:

Assessment of Local Safety and Tolerability – physician and subject

The assessment of local safety and tolerability will comprise signs assessed by the (sub)investigator and symptoms reported by the subject. The signs and symptoms are not required to be reported as AEs.

At all treatment phase visits (as indicated in section 8.1), the (sub)investigator will assess application site reactions for the following signs: perilesional erythema, perilesional oedema, perilesional dryness, and perilesional erosion. The subject will assess the symptom 'application site burning or pain'.

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.

The area for the subject to assess application site burning or pain is the treatment area, including the band of skin within two (2) cm from the border of the area. The reported symptoms must be present in this area, but may extend beyond it in a continuous manner.

For each sign and symptom the highest (worst) skin reaction score across all treatment areas will be recorded by use of the following 4-point scale as specified in Table 6 (Physician's assessment) and Table 7 (Subject's assessment) respectively:

Table 6: Skin Reaction Scores – Physician's Assessment

	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

Table 7: Skin Reaction Scores – Subject's Assessment

	0 = absent	**1 = mild**	**2 = moderate**	**3 = severe**
Application site burning or pain:	No burning or pain after application	Slight, barely perceptible burning or pain after application	Distinct burning or pain after application	Marked, intense burning or pain after application

For the subject assessment of application site burning or pain, the (sub)investigator will explain the categories of the scale to the subject and the subject will tell the (sub)investigator which category to mark.

8.12 Laboratory Assessments

For both blood analysis and urinalysis, the Central Laboratory will provide the materials and instructions necessary for the collection and transportation of the samples.

8.12.1 Safety Laboratory Blood Analysis

Blood samples (27.5 ml) for biochemistry must be collected at the time points specified in the schedule of trial procedures (section 8.1).

Because there will be no repeated blood sampling, venepuncture will be used rather than indwelling catheters to minimise subject discomfort and to reduce the extent of invasive procedures.

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

Biochemistry

The following analysis will be performed on the serum blood samples:

- Calcium – in samples collected at baseline (Visit 1), after 4 weeks (Visit 2) and at the end of trial (Visit 15, or at withdrawal from trial), plus at FU1 Visit if applicable
- Albumin - in samples collected at baseline (Visit 1), after 4 weeks (Visit 2) and at the end of trialt (Visit 15, or at withdrawal from trial), plus at FU1 Visit if applicable
- 25-OH vitamin D - at baseline (Visit 1) only

Albumin-corrected serum calcium will be calculated in mmol/L using the formula:

Serum calcium (total) in mmol/L + (0.02 x [40-serum albumin in g/L]).

The (sub)investigator must evaluate all results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date. If any of the laboratory results are abnormal and judged as clinically significant, it should be recorded as an adverse event and the (sub)investigator should follow up with the subject as clinically appropriate.

If the albumin-corrected serum calcium result is above the normal reference range at Visit 2, sampling should be repeated at the next visit. If the albumin-corrected serum calcium result is above the reference range at the last on-treatment visit, a follow-up visit should be performed for repeat sampling.

For subjects undergoing ACTH challenge test (Assigned sites only)

Adrenal function testing will be undertaken in a subset of randomised subjects with psoriasis affecting between 10 and 30% of the BSA. The aim is to include 25 subjects undergoing HPA axis testing after 52 weeks of exposure.

The samples listed above will be taken before the ACTH-challenge test that is also scheduled for these visits.

The t=0 (baseline) measurement of serum cortisol concentration for the ACTH-challenge test will be made from the biochemistry sample.

The ACTH-challenge test will be performed at baseline (Visit 1), after 4 weeks (Visit 2), after 28 weeks (Visit 8) and at the end of trial (Visit 15 or at early withdrawal). If the subject withdraws prior to completing the initial open-label treatment phase, the ACTH-challenge test scheduled for Visit 2 should not be performed. If the subject discontinues the trial prior to week 56 (this also includes discontinuation due to not achieving 'clear' or 'almost clear' disease status following 4 weeks of once daily treatment following a relapse in psoriasis status), a follow-up visit must be scheduled within 7 days of the last treatment period visit for the purpose of performing the ACTH-challenge test, if the test was not perfomed on the same day (rescheduling required due to the time dependancy of the ACTH-challenge test).

Subjects will not be included in this procedure of the trial if one of the following applies to the serum cortisol concentration at Visit 1:

- ≤5 mcg/dl pre-stimulation (before CORTROSYN® / Synacthen® injection)
- ≤18 mcg/dl at 30 minutes after CORTROSYN® / Synacthen® injection

If the ACTH challenge test at Visit 15 (end of maintenance phase) or at early withdrawal shows a serum cortisol concentration ≤18 mcg/dl at both 30 minutes and 60 minutes after the ACTH challenge, a further ACTH-challenge test is required 4 weeks later (FU2 visit).

If the results of the ACTH-challenge test at the FU2 visit continue to show a serum cortisol concentration ≤18mcg/dl at both 30 minutes and 60 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 or at 60 minutes after the ACTH challenge, or at both time-points). The data from such further ACTH challenge tests must be captured in the unscheduled follow-up visit page in the eCRF.

The following procedures should be performed prior to the ACTH challenge tests: Heart rate and blood pressure, blood/urine sampling for central laboratory analysis (biochemistry/urinalysis), blood sampling for biomarkers and urine pregnancy test (in female subjects of child-bearing potential).

To perform the ACTH challenge test, a 2.5 ml sample of venous blood will be drawn at 08.00 a.m. ±30 minutes. This sample is also the one on which the biochemistry analyses are performed, as detailed above. Within 10 minutes after blood sampling, CORTROSYN® / Synacthen® will be injected, as described in section 10.9. Two further 2.5ml 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 stop time of CORTROSYN® / Synacthen® injection will be recorded in the eCRF.

ACTH challenge tests will require the subject's specific consent.

8.12.2 Safety Urinalysis

A 10 - 15 ml spot urine sample will be collected at baseline (Visit 1), week 4 (Visit 2) and at the end of trial (Visit 15, or at withdrawal from trial), plus at FU1 Visit if applicable.

The laboratory will report:

- Calcium
- Creatinine
- Calcium:creatinine ratio will be calculated.

The (sub)investigator must evaluate all calcium:creatinine ratio results outside the reference range (‘clinically significant’ or ‘not clinically significant’) and sign and date. If any of the calcium:creatinine ratio results are abnormal and judged as clinically significant, it should be recorded as an AE.

If the calcium:creatinine ratio result is above the normal reference range and judged as clinically significant at Visit 2, sampling should be repeated at the next visit. If the result is above the reference range at the last on-treatment visit and judged as clinically significant by the investigator, a follow-up visit should be performed for repeated sampling.

8.12.3 Pharmacodynamic (PD) Assessments

8.12.3.1 Blood sampling for serum biomarkers (for consenting subjects)

Blood samples will be drawn at Visit 1 (baseline), Visit 8 (Week 28) and Visit 15 (end of trial or earlier in case of early withdrawal in subjects who have completed at least 40 weeks of the trial from baseline) for analysis of biomarkers related to systemic inflammation, cardiovascular disease, and metabolic syndrome. Initially, baseline and end of trial samples from the 50 subjects with highest baseline disease score will be analysed. Depending on the results from this analysis, the remaining samples may be analysed using a more focused biomarker panel. The analysis will be performed at the Biomarker Laboratory after unblinding of the trial, and the results will be described in a separate report. The Central Laboratory will provide the materials for the collection and the Biomarker Laboratory will provide instructions necessary for the handling and transportation of the samples.

The blood volume will not exceed 24 ml (8 ml at baseline, 8 ml at Week 28 and 8 ml at end of trial or earlier in case of early withdrawal in subjects who have completed at least 40 weeks of the trial from baseline).

LEO will collect and store half of this blood volume for future use (i.e., for analyses not described above). The sample will be stored in the bio bank established by LEO. The samples will be used for future research performed by LEO. Collection, storage and future use of the samples will require the subject's consent and donation. Donation of the samples for future research is voluntary and subjects must give their separate written consent to confirm the donation and the terms associated herewith.

8.12.4 Total Blood Volume

The blood volumes drawn per subject for the different analyses are shown in Table 8.

Table 8: Blood volume drawn from each subject during the trial

	Baseline	Week 4	Week 28	End of Trial	Total
Vitamin D	5 ml				27,5 ml
Calcium and albumin	7,5 ml	7,5 ml		7,5 ml	
Biomarker[1]	8 ml		8 ml	8 ml	24 ml
ACTH challenge test[1,2]	5 ml	5 ml	7,5 ml	5 ml	22,5 ml

1) Optional; requires separate consent by the subject

2) Selected sites only. Note that T=0 measurement of serum cortisol at Baseline, Week 4, and End of Trial will be made from the biochemistry sample.

The total blood volume collected during the trial will for most subjects not exceed 50 ml. Only if subjects participate in both the biomarker and the HPA axis part of the trial, will the volume exceed 50 ml, but will not exceed 100 ml.

8.13 Patient Reported Outcomes

The subject must make self-assessments of quality of life and health status/symptoms at visits specified in the schedule of trial procedures (section 8.1). To ensure unbiased answers, the PROs should be completed prior to other assessments on the day of completion of the questionnaires (when questionnaires are completed during the trial visits) and the site staff should not challenge the subject's answers. However, the subjects should be encouraged to answer all questions in the questionnaires.

The DLQI, EQ-5D-5L-PSO and WPAI:PSO will be completed at the trial site on an electronic slate/tablet. The PSI will be completed on an eDiary device, which will be provided for the subjects for use at home.

Symptoms reported on the DLQI, EQ-5D-5L-PSO, WPAI:PSO and PSI will not be captured as AEs, unless they are specifically mentioned as an AE by the subject when they are asked the non-leading question: "How have you felt since I saw you last?".

However, the site should review the PRO responses and follow up with the subject if the subject e.g. indicates a different level of anxiety/depression than what the subject answers to the above-mentioned non-leading question, in order to ensure that the subject gets the proper

help at the trial site or is referred to / encouraged to seek help from e.g. his/her primary care physician.

DLQI, EQ-5D-5L-PSO, WPAI:PSO and PSI data will be reported in the clinical trial report.

The questionnaires should preferably be completed in the below sequence.

8.13.1 DLQI

The DLQI is a validated, patient-reported, 10-item questionnaire that captures the effects of dermatologic conditions on a patient's health-related quality of life (HRQoL). The questions evaluate daily activities, symptoms and feelings, leisure, work or school, personal relationships, and treatment.

The DLQI will be completed by the subject at the trial site at baseline (Visit 1), at all monthly visits during the maintenance phase, and at all unscheduled visits (see Appendix 8: DLQI).

8.13.2 EQ-5D-5L-PSO

The EuroQoL-5D-5L is a standardized, preference-based, non–disease-specific instrument for describing and valuing HRQoL (see Appendix 7: EQ-5D-5L-PSO). Its components include a questionnaire on five general health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and two psoriasis-related health dimensions (skin irritation and self-confidence) each with five response levels, and a VAS represented on a thermometer that allows patients to assess their health status with a score ranging from 0 (worst health) to 100 (best health). Responses to the questions on the five dimensions result in a health state that can be converted into an index score based on the valuation of EuroQoL-5D health states from general population samples. The index score ranges from 0.00 to 1.00, where a score of 1.00 indicates full health and a 0.05 change is considered clinically meaningful.

EQ-5D-5L-PSO will be administered at baseline (Visit 1) and at all monthly visits during the maintenance phase, as well as at all unscheduled visits. This questionnaire will be filled out by the subject at the trial site.

8.13.3 WPAI:PSO

The impact of the psoriasis on subject's ability to work and perform regular activities will be assessed by means of the Work Productivity and Activity Impairment: Psoriasis (WPAI:PSO) questionnaire (see Appendix 9: WPAI:PSO).The Work Productivity and Activity Impairment

Questionnaire Specific Health Problem (WPAI-SHP) is a validated instrument that has been used to study the impact of various diseases, including psoriasis, on patients' ability to work and perform daily activities. It can be used to assess the work productivity and activity impairment related to a variety of diseases, including psoriasis. It consist of 6 questions that measure work productivity and activity impairment related to skin psoriasis. Following the standard methodology, the following measures can be constructed from the questions: (1) current employment status; (2) absenteeism, defined as the percentage of time missed from work as a result of the disease; (3) presenteeism, defined as the percentage reduced productivity while working; (4) total activity impairment (TAI), defined as the percentage impairment in regular daily activities other than work; and (5) total work productivity impairment (TWPI), representing the total percentage of work impairment associated with psoriasis from both absenteeism and presenteeism. The percentage of impairment associated with psoriasis will be assessed by each patient.

This questionnaire will be administered at baseline (Visit 1), at randomisation (Visit 2/Week 4), after approximately 6 months (Visit 8/Week 28) and at the end of trial (Visit 15/Week 56). This questionnaire will be filled out by the subject at the trial site.

8.13.4 Psoriasis symptom inventory (PSI)

The PSI, an eight-item measure to assess the severity of psoriasis symptoms will be completed by subjects daily during the initial open-label treatment phase (starting at Visit 1) and then weekly during the first 28 weeks of the maintenance phase (Weeks 4 to 32 (Visits 2 to 9)) and the 2 last weeks of the maintenance phase (Week 54 to 56 (Visits 14 to 15) - only applicable for completers).

The eight symptoms include itch, redness, scaling, burning, cracking, stinging, flaking and pain. 'Scaling' refers to the skin forming plates or scales that represent compacted desquamated layers of stratum corneum, which may then peel off; 'flaking' refers simply to loss of dry skin cells. Subjects rate the severity of each symptom on a 5-point Likert-type rating scale ranging from 0 (not at all) to 4 (very severe). Individual item scores are summed for a total score, which ranges from 0 to 32. The PSI will be administered as a 24-h recall version during the initial open-label treatment phase and as a 7-day recall version during the maintenance phase (the 7-day version was previously shown to provide results equivalent to 24-h recall version (22) (see Appendix 10: Psoriasis Symptom Inventory (PSI) – 24 hours recall and Appendix 11: Psoriasis Symptom Inventory (PSI) – 7 days recall respectively).

At baseline (Visit 1) the subject will complete this questionnaire in the eDiary while at the trial site. The subject will then subsequently fill this out while at home for all other timepoints/periods.

8.13.5 Subject's Global Assessment of Disease Severity

This assessment will be made from baseline (Visit 1) and at all monthly visits during the maintenance phase, as well as all unscheduled visits, based on the condition of the disease at the time of the evaluation and not in relation to the condition at a previous visit, by use of the 5-point scale specified below in Table 9. This assessment has to be done before investigator's assessments. The (sub)investigator will explain the categories of the scale to the subject and the subject will tell the (sub)investigator which category to mark.

Table 9: Disease Severity Grading – Subject's Assessment

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 with or restricts daily life very frequently

8.14 Subject assessment of local safety and tolerability

As stated in section 8.11, the assessment of local safety and tolerability will also include symptoms reported by the subject. The symptoms are not required to be reported as AEs.

See section 8.11 for more details.

8.15 Photography

At a limited number of pre-selected trial sites, the target lesion/location selected for the Investigator's Assessment of the Severity of the Target Lesion/Location (Redness, Thickness, Scaliness) may be photographed.

Photographs will only be taken for subjects where additional photograph-specific informed consent has been obtained. Participating in the imaging assessments is entirely voluntary, and subjects who do not wish to have images collected will still be invited to participate in the trial without being part of the trial sub-population from which images are collected.

The designated sites will use their own equipment to take colour photographs and these imaging assessments will be performed according to local regulations.

Photographs will only be taken of the psoriasis target lesion/location affecting the trunk and limbs and the images will only be used as supportive data to the clinical assessments (i.e. there will be no adjudication of images or statistical analysis).

Subjects' name or other identifying information will not be used in the trial photographs or in any later use of the photographs.

Images will be collected at each trial visit. The recommendation of images to be collected includes:

- Anatomical Image, used to confirm the location of the target lesion/location
- Macro Image

The location of the target lesion/location will be recorded by means of a visual representation in the source records and printed copies of the photographs must be included as part of the individual subject source documentation.

LEO may at its discretion use the photographs in publications, posters and similar types of information material or media targeting patients and health care professionals. The photographs can also be part of training material used for training and educational purposes.

8.16 Investigator Assessments

All dermatologic assessments of the treatment area must be performed by a dermatologist, certified physician’s assistant, advanced registered nurse practitioner or general practitioner experienced in treating psoriasis vulgaris. The same person should attempt to perform all dermatologic examinations of each individual subject.

8.16.1 Definition of the body areas to be assessed (treatment areas)

The body areas which are to be assessed are the trunk and limbs.

The trunk and limbs includes the arms* and trunk** and the legs***.

*) arms include the back of the hands
**) trunk includes the neck
***) legs include the buttocks and the top of the feet

The face, scalp, genitals and skin folds (i.e. the axillae, the inguinal folds, the inter-gluteal folds and the infra-mammary folds) are not to be treated with the IPs or assessed as part of the efficacy analysis. Also palms and soles are excluded.

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

8.16.2 Physician's Global Assessment of Disease Severity (PGA)

From screening , and at all monthly visits during the maintenance phase, as well as all unscheduled visits, the (sub)investigator will make a global assessment of the disease severity of psoriasis of the trunk and limbs using the 5-point scale specified in Table 10. This assessment will represent the average lesion severity on the trunk and limbs. 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 10: Disease Severity Grading – Physician's Assessment

Clear (=0)	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 (=1)	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 colouration
Mild (=2)	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red colouration
Moderate (=3)	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red colouration
Severe (=4)	Plaque thickening = marked elevation typically with hard or sharp edges Scaling = non-tenacious scale predominates, covering most or all of the lesions Erythema = very bright red colouration

Note: At Day 0 (Visit 1) disease severity must be graded as at least 'Mild' in order to meet inclusion criterion No. 6.

8.16.3 Physician's Assessment of the Extent and Severity of Clinical Signs (Redness, Thickness, Scaliness) (m-PASI)

From baseline (Visit 1), and at all monthly visits during the maintenance phase, as well as all unscheduled visits, the (sub)investigator will make assessments of the extent and severity of clinical signs of the subject's psoriasis. Assessment is not made for the head (i.e. the face and scalp). Hence, this PASI assessment is modified to exclude the head.

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

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

This assessment of extent is the percentage of that body area that is affected, and **not** the percentage global BSA affected (see section 8.16.4). 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).

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

Redness

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

Thickness

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

Scaliness

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

PASI:

The following formula will be used to calculate the m-PASI:

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 X + Y + Z gives the m-PASI which can range from 0 to 64.8.

8.16.4 Investigator's Assessment of the Body Surface Area (BSA) Involvement of Psoriasis Vulgaris on Trunk and Limbs

From baseline (Visit 1), and at all monthly visits during the maintenance phase, as well as all unscheduled visits, the (sub)investigator will assess the extent of the subject's psoriatic involvement on the trunk and limbs. The total psoriatic involvement on the trunk and limbs (excluding skin folds and genitals) will be recorded as a percentage of the total BSA, estimating that the surface of the subject's full, flat palm (including the five digits) correlates

to approximately 1% of the total BSA. The purpose of this is to obtain an estimate of the area on the trunk and limbs to be treated with trial medication.

8.16.5 Investigator's Assessment of the Severity of the Target Lesion/Target Location (Redness, Thickness, Scaliness)

At Visit 1 (baseline), the (sub)investigator will select a target lesion/target location. The target lesion/location should be at least 3 cm at its longest axis located on the body (i.e., not on the scalp, face or intertrigious areas). The location will be recorded in the eCRF as trunk, limb excluding elbow/knee, elbow or knee, and in more detail in the subject medical records to allow identification of the target lesion/location at subsequent visits.

From baseline (Visit 1), and at all monthly visits during the maintenance phase, as well as all unscheduled visits, the (sub)investigator will assess the severity of the target lesion/location for each clinical sign (redness, thickness, scaliness) according to the same scale as for the Investigator's Assessment of the Severity of Clinical Signs (redness, thickness, scaliness). At Visit 1, the scoring of the target lesion/location should be at least 1 for each of redness, thickness and scaliness, and at least 4 in total (see section 8.16.3 for scores).

8.17 Dispensing of IP

Refer to section 10.7.1

8.18 Return of IP and Compliance

Refer to sections 10.7.1 and 10.7.3

8.19 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 in Appendix 4: Definitions of Adverse Events and Serious Adverse Events
- Classification of AEs in terms of severity, causality and outcome are defined in Appendix 5: Classification of Adverse Events.

9.1 Collection of Adverse Events

AEs, including events of rebound, must be collected from time of first trial-related activity after the subject has signed the informed consent form until the FU3 visit. Refer to section 11.3.6.2 for a definition of rebound.

Abnormal findings observed at the screening visit should be recorded as diagnoses in the Concomitant Medication page if medication is currently being taken for the condition. If not, it will be documented as medical history in the eCRF.

AEs must be assessed by medically qualified personnel.

At all visits during the treatment phases, the subject will be asked a non-leading question by the (sub)investigator about AEs, for example: “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.

9.1.1 Application site reactions: Assessment of local safety and tolerability

Application site reactions (perilesional erythema, oedema, dryness, erosion and burning and pain) which match the criteria in the Local Safety and Tolerability Scale (see Section 8.11) are not to be reported as AEs in the eCRF even if they require treatment. Application site reactions other than those identified in the Local Safety and Tolerability scale must be recorded appropriately as AEs. Any application site reaction classified as SAEs must be added to the AE form in the eCRF and in addition reported to LEO on the SAE Form (according to “Investigator Reporting Responsibilities”, Section 9.4.1). Any treatment for an application site reaction must be recorded on the concomitant medication page of the eCRF.

9.2 Reporting of Adverse Events in the eCRF

AEs reported by the subject or observed by the (sub)investigator must be recorded on the AE form of the eCRF 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 e.g. the face, scalp, back, chest, arm, leg, trunk or limb.

Additionally, the location should be described using the following terminology:

- Lesional/perilesional (≤ 2 cm from the area(s) treated with IPs) or
- distant (>2 cm from the area(s) treated)

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 5: Classification of Adverse Events.

9.2.1 Additional requirements for reporting of adverse events of concern associated with long-term topical corticosteroid use

If the (sub)investigator considers an AE to be one of concern associated with long-term topical corticosteroid use, this should be indicated in the AE section of the eCRF, and will require a detailed narrative of the AE to be entered, including a description of the clinical course, the area(s) affected if a cutaneous event (body location and approximate size), and predisposing concomitant conditions, medications, or history.

If LEO suspects that an AE may be one of concern associated with long-term topical corticosteroid use, LEO may ask the (sub)investigator to provide additional information.

The purpose of collecting these additional data is to provide as much information as possible on suspected events in order to aid the adjudication of events by the Adjudication Panel.

9.2.2 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, drug interrupted, drug withdrawn, not applicable, unknown).

Note regarding AEs of concern associated with long-term corticosteroid use: A (sub)investigator may consider an AE to be one of concern associated with long-term topical corticosteroid use and may wish to manage such an event by temporarily or permanently stopping trial medication usage. Such a change in trial medication usage may apply to just the area(s) affected by the event, or its total use. Such a change in trial medication usage must be documented in the eCRF.

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.

9.3 Other Events to be Reported

9.3.1 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 (GPV), LEO (see section 9.4.1 for contact details).

Please also confer with section 7.9, Discontinuation.

9.3.2 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.

In this clinical trial, the use of more than one 60g can in 4 days is considered an overdose.

The term overdose must be documented on the AE form in the eCRF. In addition, AEs originating from overdose must be documented on a separate line.

9.3.3 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 AE form in the eCRF. In addition, AEs originating from a medication error must be documented on a separate line specifying the category of error (see definitions above).

9.3.4 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 AE form in the eCRF. In addition AEs originating from misuse must be documented on a separate line.

9.3.5 Abuse

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

The term abuse must be documented on the AE form in the eCRF. In addition, AEs originating from abuse must be documented on a separate line.

9.3.6 Aggravation of Condition

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

Relapse of psoriasis during the maintenance phase of the trial or during the follow-up phase should not be reported as an AE. Rebound effect (defined as (i) an m-PASI ≥12 AND an increase in m-PASI of ≥125% of the baseline value, or (ii) new pustular, erythrodermic or more inflammatory psoriasis either a) within 2 months after discontinuation of once-daily treatment in the initial open-label phase, b) within 2 months after discontinuation of once-daily relapse treatment, or c) within 2 months after end of maintenance treatment (up to Visit FU3)) must be reported as an AE.

9.3.7 Lack of Efficacy

Not applicable.

9.3.8 Adverse Events of Special Interest

None. For AEs of concern associated with long-term corticosteroid use, see sections 9.2.1 and 9.2.2.

9.4 Additional Reporting Requirements for Serious Adverse Events

9.4.1 Investigator Reporting Responsibilities

Any Serious Adverse Event (SAE) must be reported to LEO on the (paper) SAE 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 IPs, 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 GPV, LEO using the following fax number or e-mail address:

Fax number: +45 7226 3287

E-mail address: drug.safety@leo-pharma.com

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

Additionally, GPV, LEO may request further information in order to fully assess the SAE. The (sub)investigator must forward such information to GPV, 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 GPV, LEO (drug.safety@leo-pharma.com) if the (sub)investigator becomes aware of them.

9.4.2 LEO Reporting Responsibilities

GPV, LEO is responsible for assessing whether or not a SAE is expected. The relevant reference document for this clinical trial is:

LEO 90100 aerosol foam: the LEO 90100 Investigator's Brochure, edition 7 (11) and subsequent updates.

GPV, 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 which are assessed as causally related to the IP(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.

9.5 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 has completed the FU3 visit, AEs classified as possibly or probably related to the IPs should be followed for 14 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.

If a rebound is confirmed at a FU3, the subject will be followed up for 14 days or until resolution, whichever occurs first, unless the event is considered an SAE.

10 Investigational Product(s)

10.1 Investigational Product Description

The IPs are described in Table 11 and Table 12 respectively.

Table 11: Description of Enstilar®/LEO 90100 Aerosol Foam

Finished product (brand) name/name investigational product	Enstilar®/LEO 90100 aerosol foam
Formulation	Aerosol foam
Active ingredient name/concentration	Calcipotriol 50 mcg/g (as hydrate) and betamethasone 0.5 mg/g (as dipropionate)
Excipients	Paraffin, white soft; Paraffin, liquid; Polyoxypropylene stearyl ether; all-rac-alpha-tocopherol; Dimethyl ether; Butane; Butylhydroxytoluene (E321) CCI [redacted]
Pack size(s)	60 g
Manufacturer of bulk medication (IP)	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 and LEO Laboratories Ltd, 285 Cashel Road, Dublin 12, Ireland
Certifier of IP in primary packaging	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark
Manufacturer of secondary packaging and labeling	Klifo Smedeland 36, 2600 Glostrup, Denmark
Certifier name of Secondary packaging and labeling	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark

Table 12: Description of Enstilar® vehicle/LEO 90100 Aerosol Foam Vehicle

Finished product (brand) name/name investigational product	Enstilar® vehicle/LEO 90100 aerosol foam vehicle
Formulation	Aerosol foam
Active ingredient name/concentration	Not applicable
Excipients	Paraffin, white soft; Paraffin, liquid; Polyoxypropylene stearyl ether; all-rac-alpha-tocopherol; Dimethyl ether; Butane; Butylhydroxytoluene (E321) CCI [redacted]
Pack size(s)	60 g
Manufacturer of bulk medication (IP)	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 and LEO Laboratories Ltd, 285 Cashel Road, Dublin 12, Ireland
Certifier of IP in primary packaging	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark
Manufacturer of secondary packaging and labeling	Klifo Smedeland 36, 2600 Glostrup, Denmark
Certifier name of Secondary packaging and labeling	LEO Pharma A/S, Industriparken 55, 2750 Ballerup, Denmark

10.2 Administration of Investigational Products

The administration of IP is described in Table 13.

Table 13: Administration of Investigational Products

Route of administration	Topical
Dosing range	Not applicable
Dosing frequency	**Initial open-label treatment phase**: LEO 90100 once daily for 4 weeks **Maintenance phase**: randomised maintenance IP twice weekly 3 or 4 days apart. **In case of relapse**: Rescue IP once daily for 4 weeks on active lesions.
Weekly maximum	**Initial open label phase**: 100 g per week **Treatment of relapse**: 100 g per week for daily treatment **Maintenance phase**: 30 g per week (15 g per day)
Time of day for dosing	No specific requirements
Relation of time of dosing of rescue IP and maintenance IP during relapse (on days requiring application of both IPs)	Maintenance IP before rescue IP
Relation of time of dosing to clinical assessments	Preferably no dosing within 2 hours prior to the site visit

At Visit 1, the subject will be given a treatment instruction sheet describing the scenarios to be considered depending on the different treatment phases and they will receive verbal instruction about how to apply the trial medication.

- During the initial open-label treatment phase, subjects will be asked to apply LEO 90100 once daily on the affected areas on trunk and limbs for 4 weeks. At Visit 2 (after 4 weeks), subjects will have to return all containers with trial medication and, if they have achieved treatment success (PGA score of ‘clear’ or ‘almost clear’ with at least a 2-grade improvement from baseline), they will be dispensed new (blinded) medication according to the randomisation scheme.

- During the maintenance phase, subjects will apply maintenance IP twice weekly on trunk and limbs to areas where lesions have cleared or almost cleared after treatment was initiated at baseline. Any new psoriatic lesions that have been cleared by rescue treatment during relapse phase should be treated with maintenance IP as well. The treatment should be applied 3 or 4 days apart. The choice of the application days (two days) should be left to subjects' preference (e.g., Thursday and Sunday); these days will be fixed at Visit 2, recorded in the eCRF and subjects will be asked to keep the selected days throughout the trial. To improve medication adherence, electronic reminders will be sent to the subject every week on the selected application days.
- Following confirmation of a relapse during the maintenance phase, subjects will be asked to apply rescue IP once daily on the active psoriatic lesions on trunk and limbs for 4 weeks, while continuing twice-weekly maintenance treatment on non-active lesions. Rescue IP will be dispensed at the visit when relapse is confirmed. The rescue IP will be stopped after 4 weeks at a scheduled visit or at a relapse follow-up visit, as applicable.

The first application of the IP should be made under supervision and instruction of a member of the trial staff or at home the same day the subject attended Visit 1. The IPs will be dispensed by a designated person. As described above, there will be different types of instructions for initial open-label, maintenance and relapse treatment phases. Subjects will always be reminded which instruction(s) to follow during the next 4-week period.

When an application is to be administered on the same day as a trial visit, it should not be administered within 2 hours of the site visit.

Missed application during the maintenance phase:

LEO 90100 should be applied twice weekly 3 or 4 days apart on specific days. If an application is missed, the medication should be applied as soon as subject remembers. The next application should be made at the next scheduled dosing date.

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

IPs will be supplied in bulk kits.

During the initial open-label treatment phase, each subject will receive the necessary supplies for 4 weeks (7 cans of LEO 90100). These cans will be dispensed at Visit 1.

Then, every 4 weeks during the maintenance phase subjects will receive the necessary supplies (3 cans of maintenance IP), which is sufficient for the visit interval when used twice per week. These kits will be dispensed at each scheduled visit until the end of the trial.

In total, at least 14 dispensations will be made per subject over the duration of the trial (7 cans will be dispensed at Visit 1, and 3 cans will be dispensed at each visit from Visit 2 to Visit 14).

In addition, in case of relapse during the maintenance phase, the subject will receive the necessary supplies (7 cans of rescue IP) to be treated once daily on the active lesions for 4 weeks.

During relapse treatment subjects may also be in maintenance treatment on areas where psoriasis is not active. To distinguish the rescue IP from the maintenance IP, the products are colour coded as follows:

- Open-label (initial or rescue) IP: yellow labels
- Double-blind (maintenance) IP: white labels

The labelling of trial products must be in accordance with Annex 13, local regulations and trial requirements.

Immediate Treatment Packaging - Individual Unit

The primary packaging for the IPs consists of an aluminium can into which the formulation is pre-filled and subsequently administered through a continuous valve. Each individual can contains 60 g of IP. Primary and secondary packaging materials will be individually labelled in accordance with local regulations.

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:

For United States:

- Store at 20-25 °C. Excursions between 15-30°C permitted.
- Contents under pressure. Do not puncture or incinerate.
- Do not expose to heat or store at temperatures above 120°F (49°C). Do not freeze.
- Flammable – avoid heat, flame or smoking when using this product.
- Keep out of the reach of children.
- Shake before use.
- Wash hands after use.

For other countries:

- Store below 30°C.
- Extremely flammable aerosol.
- Pressurised container: May burst if heated.
- Protect from sunlight.
- Do not expose to temperatures exceeding 50°C.
- Do not pierce or burn, even after use.
- Do not spray on an open flame or other ignition source.
- Keep away from sparks, open flames and other ignition sources.
- No smoking.
- Keep out of the reach of children.
- Shake before use.
- Wash hands after use.

10.6 Treatment Assignment

Subjects who have been found to comply with all the inclusion criteria and not to violate any of the exclusion criteria, and who achieve treatment success (PGA score of 'clear' or 'almost clear' with at least a 2-grade improvement from baseline) after the initial 4 week of once daily treatment with LEO 90100 will be randomised to receive treatment with either :

- LEO 90100 aerosol foam (also referred to as 'LEO 90100')
- Aerosol foam vehicle (also referred to as 'foam vehicle')

Treatment assignment will be pre-planned according to a computer generated randomisation schedule in a 1:1 ratio.

Subjects will be randomised centrally to treatment with LEO 90100 aerosol foam or LEO 90100 aerosol foam vehicle using a stratified randomisation through an Interactive Web Response System (IWRS).

Each investigator site will be supplied with sufficient trial products for the trial on an ongoing basis controlled by the IWRS. Randomisation will be stratified by trial site, HPA axis testing, and by baseline disease severity (mild, moderate, severe).

The maximum number of subjects to be included in the open-label phase with 'mild' disease according to the PGA at baseline (visit 1) is capped at 20% to ensure similar distribution of disease severity at baseline as in previous LEO 90100 short-term trials and hence similar trial population.

10.6.1 Randomisation Code List

The randomisation code lists will be generated by LEO.

During the clinical trial, the randomisation files must be kept inaccessible to staff involved with the conduct and administration of the clinical trial until the clinical trial is unblinded.

10.7 Drug Accountability and Compliance Checks

10.7.1 Drug Accountability

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

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

At each visit, the IP, including (empty) containers dispensed at the previous visit, must be returned by the subject. An inventory (Individual Drug Accountability Form) must be kept of the IP given to and returned by each subject participating 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 IP.

All IP 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 IP. Accountability must be documented by using drug accountability forms.

The IP 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 IP used between visits.

10.7.2 Trial Product Destruction

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

10.7.3 Treatment Compliance

Treatment compliance will be recorded in an eDiary.

During the open-label treatment phase, subjects will be asked to provide this information daily whereas treatment compliance will be recorded weekly during the entire maintenance phase (i.e., from Visit 2/Week 4 to the end of trial, irrespective of whether subject is on maintenance or once daily treatment).

In case of non-compliance, the reason for it should be recorded in the eDiary.

However, the (sub)investigator should remind the subject of the importance of following the instructions given including taking the trial medication as prescribed for respective phase of the trial.

The investigator (or designee) should review the compliance data entered in the eDiary before each visit, and, in case of non-compliance, remind/re-train the subject to improve compliance.

10.8 Emergency Unblinding of Individual Subject Treatment

While the safety of a subject always comes first, it is still important to seriously consider if unblinding is necessary to ensure a subject's safety. This section describes the procedures for unblinding a subject. An emergency unblinding request can be made by the investigator, (sub)investigators, other health care professionals or authorised LEO personnel.

Emergency unblinding of individual subject treatment can be achieved by contacting the IWRS CRO to obtain information regarding an individual subject's treatment assignment.

10.9 CORTROSYN® (cosyntropin) / Synacthen® (tetracosactid) 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® is a non-Investigational Medicinal Product. The applicable product will be sourced by the trial sites, except in Poland. In Poland Synacthen® will be supplied by the sponsor.

CORTROSYN® will be used in accordance with the U.S. Prescribing Information for the marketed product (see Appendix 2: U.S. Prescribing information for CORTROSYN® (cosyntronin) for injection). Synacthen® will be used in accordance with the SmPC (see Appendix 3: Summary of Product Characteristics for Synacthen® (Tetracosactide) Ampoules 250mcg)

10.9.1 CORTROSYN® and Synacthen®

Cortrosyn® is described in Table 14 and Synacthen® is described in Table 15.

Table 14: Description of 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	11570 6th Street Rancho Cucamonga, CA 91730, U.S.A.
Supplier's name	Not Applicable.
Certifier's name	11570 6th Street Rancho Cucamonga, CA 91730, U.S.A.

Table 15: Description of 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)	1 ml ampoules
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, where it will be supplied by the sponsor).
Supplier's name	See above
Certifier's name	See above

10.9.1.1 Packaging and Labelling

The marketed product, as available in the US or in Europe will be used for this trial without any re-labelling or re-packaging of the product.

In Poland trial sites will be provided the Synacthen® through the depot at Klifo in Glostrup, Denmark.

10.9.1.2 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.

10.9.1.3 Reconstitution and Administration of CORTROSYN® (in the US)

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

10.9.1.4 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 (in connection to reconstitution of CORTROSYN® (in the US)) include:

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

See the Prescribing Information for CORTROSYN® in Appendix 2: U.S. Prescribing information for CORTROSYN® (cosyntronin) for injection and for Synacthen® in Appendix 3: Summary of Product Characteristics for Synacthen® (Tetracosactide) Ampoules 250mcg for further details.

Athletes should be aware that CORTROSYN® and Synacthen® contain active ingredients that may cause a positive result on doping tests.

10.9.1.5 Drug Accountability

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

10.9.2 0.9% Sodium Chloride Injection, USP, for Reconstitution of CORTROSYN® (in the US)

0.9% Sodium Chloride Injection, USP will be sourced by the trial sites. There is no requirement for a specific brand or manufacturer to be used, however 0.9% Sodium Chloride Injection, USP is recommended for use based on the availability of an appropriate vial size for the reconstitution of CORTROSYN® as described in section 10.9.1.3.

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

10.9.2.1 Packaging and Labelling

The marketed product, as available in the United States, will be used for this trial without any relabeling or re-packaging of the product.

10.9.2.2 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.

10.9.2.3 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

10.9.2.4 Drug Accountability

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

11 Statistical Methods

The trial consists of two different periods of treatment. The subjects are enrolled in the trial at baseline. The first 4 weeks of treatment after a subject is included in the trial will be denoted the open-label treatment phase. If the subject obtains treatment success (i.e., PGA score of ‘clear’ or ‘almost clear’ with at least 2-grade improvement from baseline) at the end of the open-label treatment phase, the subject is randomised. Otherwise the subject is discontinued from the trial. The second treatment period is denoted the maintenance phase. It starts at randomisation and ends at end of trial. The randomised maintenance treatment is twice weekly treatment with either LEO 90100 aerosol foam or LEO 90100 aerosol foam vehicle. Moreover, the subjecs treated twice weekly with LEO 90100 aerosol foam is referred to as the active treatment group and those treated twice weekly with vehicle is referred to as the vehicle group.

Note that the maintenance phase consists of maintenance treatment as well as periods of 4 weeks treatment with rescue medication in case of relapse.

In the following when referring to visit it means scheduled visit although not explicity stated.

11.1 Determination of Sample Size

For subjects with psoriasis vulgaris, the number of relapses per year is assumed to be between 4 and 8. We assume that the time to event (first relapse) is a Poisson process, i.e. that events occur continuously and independently at a constant rate. Then the time between events is given by the exponential distribution. Time to event is analysed by means of the hazard function, which can be thought of as the probability of experiencing an event now if you have not experienced one already. Table 16 shows the mean and median waiting times as well as hazards according to number of relapses per year.

Table 16: Mean and median waiting times and hazards according to number of relapses per year

	Number of relapses per year		
	4	6	8
Mean waiting time (weeks)	13.00	8.67	6.50
Median waiting time (weeks)	9.01	6.01	4.51
Hazard	0.077	0.115	0.154

The drop-out rate observed in a long-term trial with calcipotriol/BDP ointment (MCB 0102 INT) was about 30 % over 52 weeks. Assuming an exponential decline this corresponds to a median waiting time for drop out at about 101 weeks. We assume that the same will be the case in this trial and that between 4 to 8 relapses will occur per year in the vehicle group.

A 30 percent reduction in hazard, i.e. a hazard ratio of 0.7 for active treatment group relative to vehicle group is considered to be of clinical interest.

With the above assumptions it follows using a two sample survival test that for detecting a hazard ratio of 0.7 for active treatment group relative to vehicle group, between 178 and 190 subjects per group are needed in order to obtain a power of 90% for a 5% significance level. Thus, 380 subjects should be randomised.

In previous trials in similar populations, approximately 48% subjects treated with LEO 90100 aerosol foam achieved treatment success after 4 weeks of treatment. Assuming a binomial distribution with 48 % probability of success it is estimated that 832 subjects should be included in the trial in order to have 90 % probability of achieving at least 380 subjects to be randomised.

For the HPA axis testing, the aim is to achieve approximately 25 subjects undergoing HPA axis testing after 52 weeks of exposure.

The total number of subjects treated in the trial should also be sufficient to comply with ICH E1 regarding long-term safety. The aim is to achieve at least 300 subjects with 26 weeks of exposure and at least 100 subjects with 52 weeks of exposure.

All randomised subjects have been exposed for 4 weeks during the open-label treatment phase. During the maintenance phase with 380 randomised subjects, assuming an exponential decline and a drop-out rate of 30 % over 52 weeks, we can expect to have 326 subjects exposed for 22 weeks and 273 subjects exposed for 48 weeks. This means that we will have 326 subjects exposed for a total of 26 weeks, and 273 subjects exposed for a total of 52 weeks.

If the actual drop-out rate is higher than the assumed drop-out rate of 30%, more subjects will be recruited and randomised to achieve at least 380 randomised subjects, including at least 300 subjects with 26 weeks of exposure and at least 100 subjects (including approximately 25 subjects undergoing HPA axis testing) with 52 weeks of exposure.

Recruitment will be stopped when a sufficient number of subjects are randomised in order to obtain the above, considering the observed randomisation and drop-out rates.

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 the clinical trial) will be accounted for in the clinical trial report.

An open-label treatment phase safety analysis set will be defined by including all subjects exposed to treatment with IP whether randomised or not.

All subjects randomised 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 International Conference on Harmonisation (ICH) E9, section 5.2.1., Full Analysis Set. If it is decided to exclude a randomised subject from the full analysis set, a justification addressing ICH E9 will be given.

A per protocol analysis set will be defined by excluding subjects from the full analysis set who:

- receive no treatment with the IPs after randomisation,
- provide no efficacy data following start of maintenance treatment,
- are known to have taken the wrong IPs throughout the maintenance phase of the trial,
- and/or do not fulfil the disease defining inclusion criteria (i.e. inclusion criteria 4, 5, 6, 7).

Further exclusion of subjects or subject data will be decided upon after a blind review of the data, reviewing all the remaining in- and exclusion criteria, but focusing on concomitant medication that may affect psoriasis vulgaris and also considering compliance/adherence and violations of visit windows.

A maintenance phase safety analysis set will be defined by excluding subjects from the full analysis set who either received no treatment with IPs following randomisation and/or for whom no post-randomisation safety evaluations are available.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the statistical analysis plan update before breaking the randomisation code.

11.3 Statistical Analysis

11.3.1 Disposition of Subjects

The reasons for leaving the trial during the open-label treatment phase will be presented for all included subjects by last visit attended.

The reasons for leaving the trial during the maintenance phase will be presented for all randomised subjects by last visit attended and by treatment group.

11.3.2 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics measured at baseline will be presented both for all subjects included in the trial, and for all randomised subjects by treatment group. Presentations of age, sex, ethnicity, race and baseline m-PASI and PGA will also be given by centre.

Demographics include age, sex, race and ethnicity. Other baseline characteristics include skin type, height, weight, body mass index and vital signs, duration of psoriasis vulgaris, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medication, previous anti-psoriatic therapy, m-PASI, physician's assessment of BSA involved, location of psoriasis, location of other psoriasis, and PGA.

11.3.3 Exposure and Treatment Compliance

11.3.3.1 Exposure

The duration of exposure to treatment in a specific visit interval will be calculated as the number of days from date of first application of IP in that period to the date of last application of IP in that period, both days included.

Duration of exposure during the open-label treatment phase will be summarized for the open-label treatment phase safety analysis set.

Duration of exposure during the maintenance phase will be summarized by treatment group for the maintenance phase safety analysis set.

For each subject, the weight of IP used for each visit interval will be determined by calculating the difference between the weight of a set of full cans dispensed and the weight of the returned cans.

The amount of IP used will be summarised for the total open-label treatment phase for the open-label treatment phase safety analysis set.

The amount of IP used will be summarised by treatment group for each visit interval and for the total maintenance phase for the maintenance phase safety analysis set.

The amount of rescue medication used will be summarised by treatment group for each visit interval and for the total maintenance phase for the maintenance phase safety analysis set.

The total amount of IP and rescue medication used will be summarised by treatment group for each visit interval and for the total maintenance phase for the maintenance phase safety analysis set.

11.3.3.2 Treatment compliance

For the open-label treatment phase, compliance with treatment instructions in terms of percentage missed applications will be summarised for the open-label treatment phase safety analysis set.

For the maintenance phase, excluding periods of treatment with rescue medication, compliance with treatment instructions in terms of percentage missed applications will be summarised by treatment group both for each visit interval and for the total maintenance phase for the maintenance phase safety analysis set.

For the periods of treatment with rescue medication during the maintenance phase, compliance with treatment instructions in terms of percentage missed applications will be summarised by treatment group for the maintenance phase safety analysis set.

11.3.3.3 Analysis of Primary Efficacy Endpoint

The primary endpoint is time to first relapse during the maintenance phase, where relapse is an exacerbation of psoriasis defined as a PGA of at least ‘mild’. This will be calculated as the number of days from randomisation to the day where the subject has the first relapse confirmed. For subjects who either do not encounter a relapse or are withdrawn from the trial, the number of days will be treated as a censored observation at the day of end of trial visit.

The number of censored and uncensored observations, i.e. number of subjects without relapse or who are withdrawn from the trial, and number of subjects with relapse, will be summarised by treatment group. The time to first relapse will be summarised by treatment group for uncensored observations, i.e. subjects with relapse.

The primary endpoint will be compared between treatments with the null hypothesis that they are equal against the alternative that they are different. The analysis will be performed both for the full analysis set (primary) and for the per protocol analysis set (supportive). The comparison will be done using a proportional hazards model with treatment group, trial site, and disease severity at baseline (as determined by the PGA) as factors. The estimate of the hazard ratio of active treatment group relative to vehicle group together with the 95% confidence interval and p-value will be presented.

The estimated survival curves with confidence intervals will be presented graphically for each of the treatment groups. Moreover the percentiles of the survivial distribution will be tabulated by treatment group.

The proportion of subjects who are still at risk for a first relapse will be compared between the two treatment groups at 26 and 52 weeks after randomisation.

11.3.3.4 Analysis of Secondary Efficacy Endpoints

The secondary endpoints will be analysed for the full analysis set, with the analysis for the per protocol analysis set being supportive. Adjustment for multiplicity will be done using the Holm-Bonferroni method (34).

11.3.3.5 Number of days in remission

The number of days in remission will be calculated for each subject as the total number of days in trial during the maintenance period minus the number of days in treatment of relapses, if any. If a subject is withdrawn from the trial for any reason, then the subject is considered not to be in remission from when the subject leaves the trial.

The number of days in remission will be summarised by treatment group.

The number of days in remission will be analysed by means of an analysis of variance (ANOVA) model with treatment group, trial site, and disease severity at baseline as factors. Estimated difference between active treatment group and vehicle group, 95% confidence interval, and p-value will be presented.

In addition, two sensitivity analyses will be performed with different handling of missing data. If a subject is withdrawn from the trial for a drug related reason (lack of efficacy, AE, did not reach remission after treatment of relapse) then in both sensitivity analyses the subject is considered not to be in remission from when the subject leaves the trial. If a subject is withdrawn from the trial for a non-drug related reason (lost to follow-up, death, other) then the data is imputed differently in the two sensitivity analyses. During the blind review of the data the withdrawal reasons specified in the ‘Other’ category should be considered and if the specified reason is judged to be drug-related it should be documented in the statistical analysis plan before breaking the randomisation code.

In the first sensitivity analysis, the subject’s observed part of the maintenance phase is assumed to be representative for the unobserved part of the maintenance phase when the subject is withdrawn due to a non-drug related reason. I.e. if the subject is in remission in 2 months out of 3 in the observed part of the maintenance phase, then it is assumed that the subject would have been in remission in 8 out of 12 months in the maintenance phase, i.e. number of days in remission is imputed to be 8 months.

In the second sensitivity analysis, the subject's last observation is carried forward (LOCF) when the subject is withdrawn due to a non-drug-related reason. I.e. if the subject is in remission the subject is considered to be in remission for the rest of the maintenance phase, and if the subject is not in remission, then subject is considered not to be in remission for the rest of the maintenance phase.

11.3.3.6 Number of relapses during maintenance phase

The number of relapses will be calculated as the sum of confirmed relapses for each subject. Subjects contribute with observed time only. The rate of relapses during the maintenance phase is assumed to be constant over time.

The number of relapses will be analysed in a Poisson regression model with treatment group, trial site, and disease severity at baseline as factors, subject as a random effect, and risk time as an offset. The risk time is the observed time at risk for each subject, i.e. the total time in trial during the maintenance phase time minus the periods of treatment of relapses, if any. The estimated incidence rate ratio for active treatment group relative to vehicle group with 95% confidence interval and p-value will be presented.

A sensitivity analysis will be performed where subjects who at some point do not achieve 'clear' or 'almost clear' after treatment of a relapse are excluded.

11.3.4 Exploratory Analysis of Efficacy

All exploratory analyses of efficacy will be analyzed for the full analysis set.

11.3.4.1 m-PASI

m-PASI will be summarised by visit and treatment group.

11.3.4.2 Subjects in remission at each visit

The number of subjects in remission at each visit will be summarised by treatment group.

11.3.4.3 Time to when PASI75 is no longer fulfilled

PASI75 will be based on the m-PASI which is calculated based on the Physician's assessment of the extent and severity of the disease locally (trunk, arms and legs) as described in section 8.16.3.

PASI75 is defined as at least 75% reduction in the modified PASI from baseline.

Only subjects who have obtained PASI75 at the time of randomisation will be considered.

The time to first time when PASI75 is no longer fulfilled will be calculated as the number of days from randomisation to the first day when the subject no longer fulfills PASI75. For subjects who either always fulfill PASI75 or are withdrawn from the trial the number of days will be treated as a censored observation at the day of the last observation.

The number of censored and uncensored observations, i.e. number of subjects who either always fulfil PASI75 or are withdrawn from the trial, and number of subjects who at some point in time no longer fulfil PASI75, will be summarised by treatment group. The time to first time when PASI75 is no longer fulfilled will be summarised by treatment group for uncensored observations.

The comparison between treatments of time to first time when PASI75 is no longer fulfilled will be done using a proportional hazards model with treatment group, trial site, and disease severity at baseline as factors. The estimate of the hazard ratio of active treatment group relative to vehicle group together with the 95% confidence interval and p-value will be presented.

The estimated survival curves with confidence intervals will be presented graphically for each of the treatment groups.

The proportion of subjects who are still at risk of not fulfilling PASI75 will be compared between the two treatment groups at 26 and 52 weeks after randomisation.

11.3.4.4 Time to first relapse according to m-PASI

Relapse according to m-PASI is included in this study in order to be able to compare with other studies where this definition is used. Relapse according to m-PASI occurs when the m-PASI level exceeds the relapse according to m-PASI level. The relapse according to m-PASI level is defined as the baseline m-PASI value minus 50% of the reduction in m-PASI obtained from the baseline visit to the randomisation visit 4 weeks later.

The time to first relapse according to m-PASI will be calculated as the number of days from randomisation to the day when the subject has the first relapse according to m-PASI. For subjects who either do not encounter a relapse according to m-PASI or are withdrawn from the trial, the number of days will be treated as a censored observation at the day of the last observation.

The number of censored and uncensored observations, i.e. number of subjects without relapse according to m-PASI or who are withdrawn from the trial, and number of subjects with relapse according to m-PASI will be summarised by treatment group. The time to first relapse according to m-PASI will be summarised by treatment group for uncensored observations.

The comparison between treatments of time to first relapse according to m-PASI will be done using a proportional hazards model with treatment group, trial site, and disease severity at baseline as factors. The estimated survival curves with confidence intervals will be presented graphically for each of the treatment groups.

11.3.4.5 Efficacy after treatment of relapse

The proportion of subjects who obtain clear or almost clear after treatment of relapse will be summarised by number of relapse (1st, 2nd, 3rd etc) for each treatment group.

11.3.4.6 Target lesion/location scores

The target lesion/location scores will be summarised over time by treatment group.

11.3.4.7 Body Surface Area (BSA)

The affected BSA will be summarised over time by treatment group.

11.3.4.8 Number of active treatment days during maintenance phase

The number of active treatment days during the maintenance phase will be presented for each treatment group.

For the active treatment group, it is the sum of days where treated with maintenance treatment (twice weekly) and days where treated with rescue medication (once daily during relapse).

For the vehicle group, it is the sum of days where treated with rescue medication (once daily during relapse).

11.3.5 Analysis of Patient-Reported Outcomes

All patient-reported outcomes will be analysed for the full analysis set for the maintenance phase and for the open-label treatment phase safety analysis set for the open-label treatment phase.

11.3.5.1 Dermatology Life Quality Index (DLQI)

A DLQI total score is the sum of the 10 equal-weighted questions and ranges from 0 (no quality of life impairment) to 30 (maximal quality of life impairment).

During the open-label treatment phase, the total DLQI score will be summarised over time.

During the maintenance phase, the total DLQI score will be summarised over time by treatment group. The total DLQI score will also be summarised over time by treatment group and relapse status, i.e. according to whether or not the subject has a confirmed relapse at that visit.

At 12 and 52 weeks after randomization the mean DLQI will be compared between treatment groups for the full analysis set using a t-test. The comparison will be done both using observed data only and using last observation carried forward. Treatment differences, p-values and confidence intervals will be presented.

11.3.5.2 EQ-5D-5L-PSO

Each of the 5 dimensions ‘mobility’, ‘self-care’, ‘usual activities’, ‘pain/discomfort’, and ‘anxiety/depression’, the index score, and each of the psoriasis bolt on dimensions (‘skin irritation’ and ‘self-confidence’) will be summarised over time by treatment group.

Health on VAS score will be summarised over time by treatment group.

11.3.5.3 WPAI:PSO

Current employment status as well as the derived measures of absenteeism, presenteeism, activity impairment and work impairment will be summarised over time both for the open-label treatment phase, and for the maintenance phase by treatment group.

11.3.5.4 Psoriasis Symptom Inventory

The total psoriasis symptom inventory score as well as each of the 8 individual scores will be summarised over time both for the open-label treatment phase, and for the maintenance phase by treatment group.

At 12 and 52 weeks after randomisation the mean total psoriasis symptom inventory score will be compared between treatment groups for the full analysis set using a t-test. The comparison will be done both using observed data only and using last observation carried forward. Treatment differences, p-values and confidence intervals will be presented.

11.3.5.5 Subject's Global Assessment of Disease Severity

The subject's global assessment of disease severity will be summarised over time by treatment group.

11.3.6 Analysis of Safety

11.3.6.1 Adverse Events

The below analyses will be performed both for the open-label treatment phase safety analysis set for the open-label treatment phase and for the maintenance phase safety analysis set for the maintenance phase. For the maintenance phase safety analysis set for the maintenance phase, AEs will be presented by treatment group.

AEs will be coded during the course of the trial according to Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred terms and primary system organ class (SOC).

Treatment emergent AEs will be summarised, however all AEs 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 IP or (applicable if there is a wash-out) if started before the first use of IP 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, AEs are defined by MedDRA preferred terms within primary SOC.

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 AEs and the number of subjects experiencing each type of AEs will be tabulated by treatment group. The percentage of subjects with AEs will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count < 5).

The severity for each type of AE will be tabulated by treatment group..

The causal relationship to trial medication for each type of AEs will be tabulated by treatment group.

Related AEs are defined as AEs for which the (sub)investigator has not described the causal relationship to IPs as 'not related'. The number of related AEs and the number of subjects

experiencing each type of related AE will be tabulated. The percentage of subjects with related AEs will be compared between treatment groups by a chi-square test or Fisher's exact test (if expected cell count < 5).

The above tabulations will be done for the total maintenance phase, for the first 28 weeks of the maintenance phase, and for the remaining 24 weeks of the maintenance phase separately. An AE will be included in the tabulations by its start date. If an AE is ongoing at Visit 2 or Visit 9 and worsened in severity after, the AE will be included in the tabulations of both affected periods.

SAEs will be evaluated separately and a narrative for each will be given.

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

11.3.6.1.1 Adverse events associated with long term corticosteroid use

The AEs which have been judged by the adjudication committee to be associated with long term corticosteroid use will be listed along with information about demography and baseline characteristics.

11.3.6.2 Rebound

Rebound will be defined as (i) an m-PASI ≥12 AND an increase in m-PASI of ≥125% of the baseline value, or (ii) new pustular, erythrodermic or more inflammatory psoriasis either a) within 2 months after discontinuation of once-daily treatment in the initial open-label phase, b) within 2 months after discontinuation of once-daily relapse treatment, or c) within 2 months after end of maintenance treatment (up to Visit FU3)

Number of rebounds within two months after entering the maintenance phase will be summarised by treatment group in a table.

Number of rebounds occurring after the first two months of maintenance treatment (i.e. including the follow-up period) will be summarised by treatment group in another table.

Subjects with m-PASI≥125% of baseline (Visit1) score and cases of rebound will be listed.

11.3.6.3 Local safety and tolerability

The local safety and tolerability signs perilesional erythema, perilesional oedema, perilesional dryness, and perilesional erosion, as well as the symptom 'application site burning or pain'

will be summarised over time both for the open-label treatment phase, and for the maintenance phase by treatment group.

11.3.6.4 ACTH-Challenge test

For the group of subjects undergoing the ACTH-challenge test, the number of subjects with serum cortisol concentration values ≤18 mcg/dl 30 minutes after the ACTH-challenge test will be summarised over time by treatment group.

11.3.6.5 Vital Signs and Physical Findings

The change in vital signs (blood pressure, heart rate, body temperature) from baseline to end of treatment phase will be summarised.

The change in vital signs (blood pressure, heart rate, body temperature) from randomisation to end of trial will be summarised.

11.3.6.6 Clinical Laboratory Evaluation

The change in each of the laboratory parameters from baseline to end of open-label treatment phase will be summarised as mean, SD, median, minimum and maximum values.

The change in each of the laboratory parameters from randomisation to end of trial will be summarised as mean, SD, median, minimum and maximum values for each treatment group.

Laboratory parameters will be classified as ‘low’, ‘normal’ or ‘high’, depending on whether the value is below, within or above the reference range, respectively.

A shift table will be produced showing the categories at baseline against those at end of treatment period.

A shift table will be produced showing the categories at randomisation against those at end of trial.

To identify subjects with clinically important laboratory changes in albumin-corrected serum calcium levels, LEO has defined threshold levels for concern for a clinically significant change based on the CTCAE v4.0 for grading of specific clinical laboratory results. These LEO-defined threshold levels correspond to a grade of at least ‘moderate’ (i.e. at least 2 on a 5-point scale) according to the CTCAE v4.0. The low threshold level for the albumin-corrected serum calcium is ‘<2.0 mmol/l’ and the high threshold level is ‘>2.9 mmol/l’.

Additional shift tables as described above will be produced for clinically significant values of albumin corrected serum calcium as defined by LEO, i.e., <2.0 mmol/l (lowthreshold) or >2.9 mmol/l (high threshold), i.e. the shift tales will be for subjects with at least one clinically significant value of albumin corrected serum calcium. .

Subjects with laboratory parameters outside the reference range will be listed.

11.3.7 Interim Analysis

No formal interim analyses are planned. However, analysis of the data from the open-label treatment phase might be performed prior to finalising the trial. This will have no impact on the continued conduct of the study nor the interpretation of the results as the open-label treatment phase is not blinded.

11.3.8 General Principles

All significance tests will be two-sided using the 5% significance level. 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).

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

All the analyses specified in the protocol will be reviewed in relation to the blinded data actually obtained and the statistical analysis plan update will be finalised before breaking the randomisation code.

The randomisation is stratified by treatment group, trial site, HPA axis testing and disease severity at baseline as factors. Usually, the statistical analysis of efficacy parameters takes all the stratification factors into account. However, the HPA axis test is a safety parameter, which is only determined at a small subset of sites and subjects. Hence stratification by HPA axis test is not applicable for all sites. Also, it is expected that two subjects per site will be randomised. This means that a statistical model having HPA axis testing as a factor may not converge, depending on whether subjects participating in the HPA axis test drop out. Furthermore, the inclusion criteria for participating in the HPA axis test are “Moderate” or “Severe” in the baseline PGA assessment and a baseline BSA between 10 and 30%. Including the stratification factor HPA axis testing would therefore introduce a confounding with the

stratification according to baseline PGA as well as sites. Therefore the stratification according to HPA axis testing is not included in the statistical analyses.

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

11.3.9 Handling of Missing Values

In the analysis of the primary endpoint, time to first relapse, missing data are treated as censored observations.

For number of days in remission in the primary analysis a subject is considered not to be in remission from when the subject leaves the trial. Two sensitivity analyses with different imputation as detailed in section 11.3.3.5 are performed.

For the secondary endpoint “number of relapses”, subjects only contribute with information until they leave the trial.

There is no imputation of missing data for the exploratory analyses of efficacy and the analyses of patient-reported outcomes.

12 Trial Committees

12.1 Adjudication Committee

A panel of 2 dermatologists and one endocrinologist (“Adjudication Panel”) will review all treatment-emergent AEs to identify AEs of concern associated with long-term use of topical corticosteroids where a causal relationship between the trial medication and the event is at least a reasonable possibility.

The Adjudication Panel will not review AEs which occurred prior to application of the first dose of IP; this includes AEs reported by screening failures (who per definition did not start open-label treatment).

The Adjudication Panel Members (APM) will be independent of the trial (i.e. they will not be participating (sub)investigators) and of LEO (i.e. they will not be LEO employees). They will also be blinded to treatment allocation at the time of the review.

A listing of AEs will be provided to the APM consisting of the following data:

- AE reported Term (as reported in eCRF).
- The MedDRA Preferred Term as coded by LEO.
- The (sub)investigator assessment of causal relationship of the use of trial medication to the event, location of cutaneous events, severity, and seriousness.
- The (sub)investigator assessment of causal relationship of long-term use of corticosteroids to the event. For such AEs of concern, the narrative recorded in the eCRF will also be provided.
- The date of onset, the outcome, and date of outcome.
- The action taken with trial medication.

The listing will be generated for patients with complete data (i.e. source data verification (SDV) and SAE reconciliation have been performed). Several listings will be generated during the trial and adjudications performed on batches of 'complete' patients, until all patients are included in this process.

The APM will be able to request eCRF pages and SAE reports on a per subject basis, should this be required for adjudication purposes.

Each APM will perform the adjudication independently of the other APMs and of LEO. If there is any discrepancies in the events identified by each APM, the APMs will discuss these, either by telephone or in a meeting. If a consensus opinion of all three APMs on identified events is not reached, a conservative approach will be used by including events adjudicated to be related to trial medication by any APM, even if identified by just one of the APMs.

The Clinical Project Manager (CPM)/National Lead Clinical Research Associate (NLCRA) is present at the time of adjudication to provide administrative support only; The CPM/NLCRA will not make any comments in relation to the adjudication of the AEs.

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 will enter subject data into eCRFs. Data recorded in the eCRFs will be accessible to the trial site and LEO personnel immediately after entry. The eCRFs must be maintained in an up-to-date state at the trial site at all times.

The investigator must verify the correctness of the data entered by the site by electronically date and sign all eCRFs used. This signature information will be kept in the audit trail and

cannot be altered. Any correction(s) made by the (sub)investigator or authorised site staff to the eCRF after original entry will be documented in the audit trail. Changes to data already approved will require the re-signature by the investigator. The person making the change to the data, and the date, time and reason for the change will be identified in the audit trail.

For archiving purposes, each investigator will be supplied with a copy of the eCRFs for all subjects enrolled at the trial site. This is done after completion of the trial and before access to the eCRF is revoked. Audit trail information will be included. eCRFs must be available for inspection by authorised representatives from LEO, from regulatory authorities and/or IEC/IRBs.

13.2 Data Handling

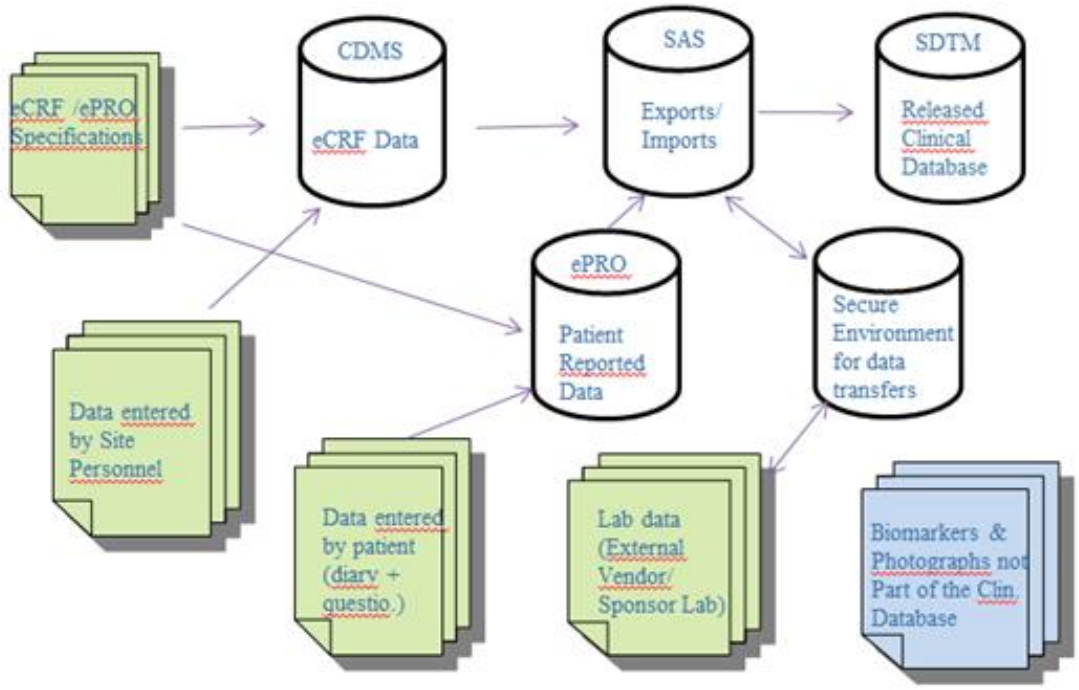
Subject data should be entered into the eCRF as soon as possible after the visit in accordance with the time requirements described in the Clinical Trial Agreement with the sites. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor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

Some PRO data will be captured electronically on a tablet/slate (ePRO) at the site. Other PRO data as well as some compliance questions will be captured on a small tablet (eDiary) by the subjects at home. By the use of ePRO and eDiary data will be available immediately after data entry and available for monitors and the site personnel, including the clinical investigator, with read access only. The investigator (or designee) is expected to review ePRO and eDiary data, and remind and re-train the subject if appropriate to ensure data completeness. The ePRO and eDiary system is a separate application from the eCRF. Data captured from the eCRF will be stored on a different servers than data captured via ePRO and eDiary during data capture. Data from both systems will be included in the final study database.

External data transfers from vendors to LEO will be transmitted and handled via a secure ftp site.

Transmissions of electronic data from external data providers and of ePRO data (including eDiary data in the below illustration) to the clinical data base is illustrated in Figure 5.

Figure 5 Flow of Electronic Data



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 eCRFs for accuracy and completeness by verifying data recorded in the eCRF 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 should as a minimum be added to the subject's medical record:

- Date(s) of conducting the informed consent process (date of enrolment) including date of provision of subject information
- Subject ID

- Randomisation code number (if applicable)
- The fact that the subject is participating in a clinical trial in psoriasis vulgaris including treatment arms of LEO 90100 or vehicle for up to 56 weeks
- Other relevant medical information
- Allocated treatment once the randomisation code has been broken (if applicable)

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 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.

Investigators will be informed when subject recruitment is to cease. This will also include information on when the threshold of 20% of subjects with a 'mild' PGA is reached, and when a sufficient number of subjects (approximately 25 subjects with 52 weeks of exposure) have been included in the HPA axis part of the trial.

Trial enrolment will be stopped at a trial site when the total requested number of subjects randomised 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.

When the randomisation code has been broken, the investigators will receive information about the treatment allocation for the subjects randomised at their respective sites and will be asked to record this in the subject's medical record.

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, 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.

Due to the design of this trial, there are no statistical criteria for trial termination.

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 (subjects should not be treated with Enstilar® until after the final follow-up visit (FU3)).

16.3 Archiving of Trial Documents

The investigator at each trial site must make arrangements to store the essential trial documents 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 revision current 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

All subjects shall receive written and verbal information concerning the clinical trial. This information will emphasise that participation in the clinical trial is voluntary and that the subject may withdraw from the clinical trial at any time and for any reason. All subjects will be given an opportunity to ask questions and will be given sufficient time to consider before consenting.

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 controller when they wish to use personal data collected in the clinical trial for their own purpose such as publication of clinical trial results.

Subjects 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 has obtained the necessary authorisations for the 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 IP(s) is confidential information of 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 IP(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 (35, 36)

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 (37) 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

ACE	Angiotensin-Converting Enzyme
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
APM	Adjudication Panel Member
BSA	Body Surface Area
CHMP	Committee for Human Medicinal Products
CMO	Contract Manufacturing Organisation
CPM	Clinical Project Manager
CRF	Case Report Form
CRO	Contract Research Organisation
DLQI	Dermatology Life Quality Index
DME	Dimethyl Ether
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EU	European Union
FDA	Food and Drug Agency
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HPA	Hypothalamic-Pituitary-Adrenal
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICTM	International Clinical Trial Manager
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
m-PASI	Modified Psoriasis Area Severity Index
NLCRA	National Lead Clinical Research Associate

PASI	Psoriasis Area Severity Index
PASI 75	A 75% reduction in the modified Psoriasis Area and Severity Index
PGA	Physician’s Global Assessment of disease severity
PRO	Patient Reported Outcome
PSI	Psoriasis Symptom Inventory
PUVA	Psoralen combined with Ultraviolet A
SAE	Serious Adverse Event
SD	Standard Deviation
SDV	Source Data Verification
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
UVB	Ultraviolet B
WMA	World Medical Association

23 Definition of terms

Throughout this document, the following terminology is used when referring to the treatment groups in the clinical trials. Please note that calcipotriol is identical to calcipotriene. Calcipotriol is the international non-proprietary name (INN) and calcipotriene is the US adopted name (USAN).

Names used in text and tables

LEO 90100	Cutaneous foam, one gram contains 50 mcg of calcipotriol (as monohydrate) and 0.5 mg of betamethasone (as dipropionate). With the propellants, this corresponds to CCI mcg of calcipotriol (as monohydrate) and CCI mg of betamethasone (as dipropionate) per gram of pressurised formulation in the can. Also referred to as LEO 90100 aerosol foam (US defined dosage form).
Foam vehicle or vehicle	LEO 90100 vehicle

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Appendix 1: Protocol Summary

Name of finished/ investigational product	LEO 90100 aerosol foam
Name of active substance	• Calcipotriol • Betamethasone dipropionate
Title of trial/trial ID/EudraCT no.	LEO 90100 twice weekly maintenance regimen for psoriasis vulgaris/LP0053-1004/2016-000556-95
Coordinating investigator(s)	Name of international coordinating investigator: Dr Mark Lebwohl
Sponsor's name/ address	LEO Pharma A/S (referred to as 'LEO' in the clinical trial protocol)
Estimated number of trial sites and distribution	Approximately 58 sites in Canada, France, Germany, Poland, United Kingdom, United States
Trial period	Planned date of enrolment of first subject: Q1-2017 Planned date of completion of last subject: Q3-2019
Main objective(s)	• To evaluate the efficacy of a twice weekly maintenance regimen with LEO 90100 compared to vehicle in the prevention of relapse in subjects with psoriasis vulgaris. • to evaluate the long-term safety of LEO 90100 (up to 52 weeks) in subjects with psoriasis vulgaris.
Methodology	This trial is a 12-month, international, multi-centre, randomised, vehicle controlled, double-blind, 2-arm, parallel group trial consisting of an initial open-label treatment phase of 4 weeks followed by a randomised, double-blind, vehicle-controlled, maintenance phase of 52 weeks in subjects with psoriasis vulgaris, and an 8-week follow-up period. After completing the open-label phase, subjects should have a disease severity (PGA) of 'clear' or 'almost clear' with at least a 2-grade improvement from baseline to continue into the maintenance phase.
Number of subjects to be enrolled	A total of 832 subjects should be included in the trial in order to have 90% probability of achieving at least 380 subjects to be randomised.

Main criteria for inclusion	• Signed and dated informed consent obtained prior to any trial related activities (including washout period) • Age 18 years or above • A clinical diagnosis of psoriasis vulgaris for at least 6 months involving the trunk and/or limbs, amenable to treatment with a maximum of 100 g of trial medication per week • Psoriasis vulgaris on the trunk and/or limbs (excluding psoriasis on the genitals and skin folds) involving 2-30% of the body surface area (BSA) • A Physician's Global Assessment of disease severity (PGA) of at least 'mild' on trunk and limbs at Visit 1 • A m-PASI score of at least 2 at Visit 1 • Females of child-bearing potential must have a negative urine pregnancy test at Visit 1 • Females of child-bearing potential must agree to use a highly effective method of birth control during the trial **<u>Additional criteria for subjects undergoing HPA axis test</u>** • Signed and dated informed consent for ACTH challenge tests • Psoriasis vulgaris on trunk and/or limbs of disease severity (PGA) of at least 'moderate' affecting between 10 and 30% of the body surface area (BSA) excluding psoriatic lesions of genitals and skin folds at Visit 1 • At Visit 1, a normal HPA axis function including a serum cortisol concentration above 5 mcg/dl before ACTH-challenge and above 18 mcg/dl 30 minutes after ACTH-challenge
Main criteria for exclusion	• Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time periods prior to Visit 1: o etanercept – within 4 weeks prior to Visit 1 o adalimumab, infliximab – within 8 weeks prior to Visit 1 o ustekinumab – within 16 weeks prior to Visit 1 o secukinumab – within 12 weeks prior to Visit 1 o other products – within 4 weeks/5 half-lives prior to Visit 1 (whichever is longer)

	• Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (e.g. corticosteroids, retinoids, methotrexate, ciclosporin and other immunosuppressants) within 4 weeks prior to Visit 1 • Systemic treatment with apremilast within 4 weeks prior to Visit 1 • Subjects who have received treatment with any non-marketed drug substance (i.e. a drug which has not yet been made available for clinical use following registration) within 4 weeks/5 half-lives (whichever is longer) prior to Visit 1 • Psoralen combined with Ultraviolet A (PUVA) therapy within 4 weeks prior to Visit 1 • Ultraviolet B (UVB) therapy within 2 weeks prior to Visit 1 • Topical anti-psoriatic treatment on the trunk and/or limbs (except for emollients) within 2 weeks prior to Visit 1 • Topical treatment on the face, scalp and skin folds with corticosteroids, or vitamin D analogues within 2 weeks prior to Visit 1 • Severe and/or extensive scalp psoriasis which, in the opinion of the investigator, requires treatment with potent or super-potent corticosteroids which will be prohibited during the trial • Pre-existing overt atrophy or teleangiectasia in treatment areas • Planned initiation of, or changes to, concomitant medication that could affect psoriasis vulgaris (e.g. beta blockers, antimalarial drugs, lithium, ACE inhibitors) during the trial • Current diagnosis of guttate, erythrodermic, exfoliative or pustular psoriasis • Subjects with any of the following conditions present on the treatment area: 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, acne vulgaris, atrophic skin, striae atrophicae, fragility of skin veins, ichtyosis, ulcers and wounds • Other inflammatory skin disorders (e.g. seborrhoeic dermatitis or contact dermatitis) on the treatment area that may confound the evaluation of psoriasis

	• Known or suspected disorders of calcium metabolism associated with hypercalcaemia Note: Additional exclusion criteria for subjects undergoing HPA axis test (assigned sites only) apply
Investigational product(s)	LEO 90100 aerosol foam, calcipotriol (as monohydrate) 50 mcg/g and betamethasone (as dipropionate) 0.5 mg/g and LEO 90100 aerosol foam vehicle (no active ingredient), for topical use • Initial open-label treatment phase: LEO 90100 once daily for 4 weeks • Maintenance phase: randomised treatment (LEO 90100 or vehicle) twice weekly, 3 or 4 days apart • Treatment of relapse: LEO 90100 once daily for 4 weeks on relapse areas, while psoriasis areas without relapse continue on maintenance
Investigational reference product(s)	Aerosol foam vehicle
Duration of treatment	• A Washout period up to 4 weeks • An initial open-label treatment phase: LEO 90100 once daily for 4 weeks • A maintenance phase: randomised treatment (LEO 90100 or vehicle) twice weekly for 52 weeks • A follow-up period of 8 weeks.
Main assessments	• Physician's Global Assessment of Disease Severity (PGA) • Physician's Assessment of the Extent and Severity of Clinical Signs (Redness, Thickness, Scaliness) (m-PASI) • Safety laboratory bood samples • Safety urinalysis • Adverse events
Primary endpoint	Time to first relapse (at least 'mild' according to the PGA)
Secondary endpoint(s)	• Number of days in remission ('clear'/'almost clear' according to the PGA) during the maintenance phase • Number of relapses during the maintenance phase

Statistical methods	**Primary endpoint** The primary endpoint is time to first relapse during the maintenance period where relapse is an exacerbation of psoriasis defined as a PGA of at least 'mild'. This will be calculated as the number of days from randomisation to the day where the subject has the first relapse confirmed. For subjects who either do not encounter a relapse or are withdrawn from the trial, the number of days will be treated as a censored observation at the day of end of trial visit. The number of censored and uncensored observations, i.e. number of subjects without relapse and number of subjects with relapse, will be summarised by treatment group. The time to first relapse will be summarised by treatment group for uncensored observations, i.e. subjects with relapse. The primary endpoint will be compared between treatments with the null hypothesis that they are equal against the alternative that they are different. The analysis will be performed both for the full analysis set (primary) and for the per protocol analysis set (supportive). The comparison will be done using a proportional hazards model with treatment group, trial site, HPA axis testing, and severity at baseline (as determined by the PGA) as factors. The estimate of the hazard ratio of active treatment group relative to vehicle group together with the 95% confidence interval and p-value will be presented. The estimated survival curves with confidence intervals will be presented graphically for each of the treatment groups. Moreover the percentiles of the survivial distribution will be tabulated by treatment group.The proportion of subjects who are still at risk for a first relapse will be compared between the two treatment groups 24 and 52 weeks after randomisation. **Secondary endpoints** The secondary endpoints will be analysed for the full analysis set, with the analysis for the per protocol analysis set being supportive. Adjustment for multiplicity will be done using the Holm-Bonferroni

	method. • Number of days in remission The number of days in remission will be calculated for each subject as the total number of days in trial during the maintenance period minus the number of days in treatment of relapses, if any. If a subject is withdrawn from the trial for any reason, then the subject is considered not to be in remission from when the subject leaves the trial. The number of days in remission will be summarised by treatment group. The number of days in remission will be analysed by means of an analysis of variance (ANOVA) model with treatment group, trial site, HPA axis testing, and severity at baseline as factors. Estimated difference between active treatment group and vehicle group, 95% confidence interval, and p-value will be presented. • Number of relapses during maintenance phase The number of relapses will be calculated as the sum of confirmed relapses for each subject. Subjects contribute with observed time only. The rate of relapses during the maintenance phase is assumed to be constant over time. The number of relapses will be analysed in a Poisson regression model with treatment group, trial site, HPA axis testing, and severity at baseline as factors, subject as a random effect, and risk time as an offset. The risk time is the observed time at risk for each subject, i.e. the total time in trial during the maintenance period time minus the periods of treatment of relapses, if any. The estimated incidence rate ratio for active treatment group relative to vehicle group with 95% confidence interval and p-value will be presented.

Appendix 2: U.S. Prescribing information for CORTROSYN® (cosyntronin) for injection

CORTROSYN®™

FOR DIAGNOSTIC USE ONLY
(cosyntropin) for Injection

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

ACTH. The sequence of amino acids in the 1 - 24 compound is as follows:

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

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

to 19 results in a 70% loss of potency.

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

The extra-adrenal effects which natural ACTH and CORTROSYN™ have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic

effect. These are considered to be without physiological or clinical significance.
Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity. This activity resides in the C-terminal portion of the molecule and the 22-39 amino acid residues exhibit the greatest degree of antigenicity. In contrast, synthetic poly-peptides containing 1-19 or fewer amino acids have no detectable immunologic activity. Those containing 1-26, 1-24 or 1-23 amino acids have very little immunologic although full biologic activity. This property of CORTROSYN™ assumes added importance in view of the known antigenicity of natural ACTH.

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

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

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

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

CONTRAINDICATION

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

PRECAUTIONS

General

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

Drug Interactions

Corticotropin may accentuate the electrolyte loss associated with diuretic therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility.

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

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

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

Pediatric Use
(See DOSAGE AND ADMINISTRATION section.)

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

- o bradycardia
- o tachycardia
- o hypertension
- o peripheral edema
- o rash

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

clinical studies and a maximal response noted with the smallest dose.

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

Two alternative methods of administration are intravenous injection and infusion. CORTROSYN™ can be injected intravenously in 2 to 5 mL of saline over a 2-minute period. When given as an intravenous infusion: CORTROSYN™, 0.25 mg may be added to glucose or saline solutions and given at the rate of approximately 40 micrograms per hour over a 6-hour period. It should not be added to blood or plasma as it is apt to be inactivated by enzymes. Adrenal response may be measured in the usual manner by determining urinary steroid excretion before and after treatment or by measuring plasma cortisol levels before and at the end of the infusion. The latter is preferable because the urinary steroid excretion does not always accurately reflect the adrenal or plasma cortisol response to ACTH.

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

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

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

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

In patients with a raised plasma bilirubin or in patients where the plasma contains free hemoglobin, falsely high fluorescence measurements will result. The test may be performed at any time during the day but because of the physiological diurnal variation of plasma cortisol the criteria listed by Wood cannot apply. It has been shown that basal plasma cortisol levels and the post CORTROSYN™ increment exhibit diurnal changes. However, the 30-minute plasma cortisol level remains unchanged throughout the day so that only this single criterion should be used (3).

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

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

Storage
Store at 15-30°C (59-86°F).

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

Rx only

REFERENCES
1. Wood, J.B. et al. LANCET 1.243, 1965.

2. Greig, W.R. et al. J. ENDOCR 34.411, 1966.

3. McGill, P.E. et al. ANN RHEUM DIS 26.123, 1967.

Amphastar Pharmaceuticals, Inc.
Rancho Cucamonga, CA 91730 U.S.A.

REV. 9-05

Appendix 3: Summary of Product Characteristics for Synacthen® (Tetracosactide) Ampoules 250mcg

1 NAME OF THE MEDICINAL PRODUCT
Synacthen Ampoules 250mcg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tetracosactide acetate 250micrograms per ampoule.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection or infusion.
A clear colourless aqueous solution for intramuscular injection or intravenous infusion in a 1 mL clear glass ampoule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Diagnostic test for the investigation of adrenocortical insufficiency.

4.2 Posology and method of administration
Adults: This preparation of Synacthen is intended for administration for diagnostic purposes only as a single intramuscular or intravenous dose; it is not to be used for repeated therapeutic administration.

The 30-minute Synacthen diagnostic test: This test is based on measurement of the plasma cortisol concentration immediately before and exactly 30 minutes after an intramuscular or intravenous injection of 250micrograms (1ml) Synacthen. Adrenocortical function can be regarded as normal if the post-injection rise in plasma cortisol concentration increases by 200 nmol/litre (70 micrograms/litre), i.e. if the value 30 minutes after injection is >500 nmol/litre (180 micrograms/litre), adrenocortical function is regarded as normal. All the plasma samples should be stored in a refrigerator until plasma cortisol level estimation.

Where the 30-minute test has yielded inconclusive results, or where it is desired to determine the functional reserve of the adrenal cortex, a 5-hour test can be performed with Synacthen Depot (see separate Summary of Product Characteristics). Furthermore, a 3-day test with Synacthen Depot may be used to differentiate between primary and secondary adrenocortical insufficiency.

Children: An intravenous dose of 250micrograms/1.73m² body surface area has been suggested. Thus for children aged 5 to 7 years, approximately half

the adult dose will be adequate. For more accurate dosing of other ages, standard body surface area tables should be consulted.

Elderly: There is no evidence to suggest that dosage should be different in the elderly.

4.3 Contraindications
Known hypersensitivity to tetracosactide and/or ACTH or to any of the excipients listed in section 6.1 List of excipients.

Synacthen is contra-indicated in patients with allergic disorders (e.g. asthma) (see Section 4.4 Special warnings and precautions for use), acute psychosis, infectious diseases, peptic ulcer, refractory heart failure, Cushing's syndrome, treatment of primary adrenocortical insufficiency and adrenocongenital syndrome.

4.4 Special warnings and precautions for use
Before using Synacthen, the doctor should make every effort to find out whether the patient is suffering from, or has a history of, allergic disorders (see Section 4.3 "Contra-indications"). In particular, he should enquire whether the patient has previously experienced adverse reactions to ACTH, Synacthen or other drugs.

Synacthen should only be administered under the supervision of appropriate senior hospital medical staff (e.g. consultants).

If local or systemic hypersensitivity reactions occur after the injection (for example, marked redness and pain at the injection site, urticaria, pruritus, flushing, faintness, severe malaise or dyspnoea), Synacthen or other ACTH preparations must be discontinued and should be avoided in the future. Hypersensitivity reactions tend to occur within 30 minutes of an injection. The patient should therefore be kept under observation during this time.

Preparation should be made in advance to combat any anaphylactic reaction that may occur after an injection of Synacthen. In the event of a serious anaphylactic reaction, the patient should be treated appropriately with adrenaline and steroids.

Synacthen Ampoules should not be used in the presence of active infectious or systemic diseases, when the use of live vaccine is contemplated or in the presence of a reduced immune response, unless adequate disease specific therapy is being given.

Use with care in patients with hypertension and thromboembolic tendencies.

Use cautiously in patients with ocular herpes simplex owing to possible

corneal perforation.

The increased production of adrenal steroids may result in corticosteroid type effects:

- Psychological disturbances may be triggered (e.g. euphoria, insomnia, mood swings, personality changes and severe depression, or even frank psychotic manifestations). Existing emotional instability or psychotic tendencies may be aggravated
- Latent infections (e.g. amoebiasis, tuberculosis) may become activated
- Ocular effects may be produced (e.g. glaucoma, cataracts)
- Dosage adjustments may be necessary in patients being treated for diabetes or hypertension
- If Synacthen is used in any of the following conditions, the risks of treatment should be weighed against the possible benefits: ulcerative colitis, diverticulitis, recent intestinal anastomosis, kidney failure, hypertension, predisposition to thromboembolism, osteoporosis, myasthenia gravis.

The solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially ‘sodium- free’.

Lack of diagnostic accuracy
Post administration total plasma cortisol levels during Synacthen test might be misleading in some special clinical situations due to altered cortisol binding globulin levels. These situations include patients on oral contraceptives, post operative patients, critical illness, severe liver disease, nephrotic syndrome. Hence in these circumstances, alternative parameters (e.g., salivary cortisol, free cortisol index, plasma free cortisol) can be used to assess the integrity of HPA axis.

4.5 Interaction with other medicinal products and other forms of interaction
Severe jaundice has been observed for concurrent use of Synacthen and valproate in paediatric population. Their concurrent use should be avoided.

Concurrent use of Synacthen and other anticonvulsants (e.g. phenytoin, clonazepam, nitrazepam, phenobarbital, primidone) may increase the risk of liver damage thus, Synacthen should be used with caution at minimum possible doses and for minimum duration for concurrent treatment.

Endogenous and synthetic oestrogens can cause an increase in total cortisol levels and therefore, it is considered appropriate to use alternative methods (e.g., salivary cortisol, free cortisol index, plasma free cortisol) for interpretation of the results of the HPA axis examination (see Section 4.4 Special warnings and precaution for use).

Since Synacthen increases the adrenocortical production of glucocorticoids and mineralocorticoids, drug interactions of the type seen with these corticosteroids may occur (see Section 4.4 Special warnings and precautions

for use). Patients already receiving medication for diabetes mellitus or for moderate to severe hypertension must have their dosage adjusted if treatment with Synacthen is started.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data in the use of tetracosactide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3 Preclinical safety data). Synacthen should be used during pregnancy only if the expected benefit outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether tetracosactide enters breast milk or not. Because many drugs are excreted in human milk, caution should be exercised when Synacthen is administered to a breastfeeding woman.

Fertility

Animal studies are insufficient with respect to reproductive toxicity (see Section 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable effects

Undesirable effects may be related to tetracosactide or to the stimulation of glucocorticoids and mineralocorticoid secretion during the use of Synacthen.

The following undesirable effects have been derived from post-marketing experience via spontaneous cases reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Undesirable effects are listed according to system organ classes in MedDRA. Within each system organ class, undesirable effects are presented in order of decreasing seriousness.

Table 1. Undesirable effects (frequency not known) related to tetracosactide

Immune system disorders:
Hypersenstivity*
Endocrine disorders:
Adrenal haemorrhage

*Tetracosactide can provoke hypersensitivity reactions, which tend to be more severe (anaphylactic shock) in patients susceptible to, allergies (especially asthma). Hypersensitivity reactions may include skin reactions at the injection site, dizziness, nausea, vomiting, urticaria, pruritus, flushing, malaise, dyspnoea, angioneurotic

oedema and Quincke's oedema.

The undesirable effects related to glucocorticoid and mineralocorticoid effects are unlikely to be observed with short-term use of Synacthen as a diagnostic tool, but may be reported when Synacthen is used in therapeutic indications. Should information be required on the side effects reported with therapeutic use of tetracosactide acetate, see Synacthen Depot Ampoules 1 mg/ml Summary of Product Characteristics.

Table 2 Undesirable effects (frequency not known) related to glucocorticoid and mineralocorticoid effects

Infections and infestations
Abscess. Infection susceptibility increased

Blood and the lymphatic system disorders
Leukocytosis

Endocrine disorders
Cushing's syndrome, secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, e.g. after trauma, surgery or illness; menstruation irregular, carbohydrate tolerance decreased, hyperglycaemia, manifestations of latent diabetes mellitus, hirsutism

Metabolism and nutrition disorders
Hypokalaemia, calcium deficiency, sodium retention, fluid retention, increased Appetite

Psychiatric disorders
Mental disorder[1)]

Nervous system disorders
Convulsions, benign intracranial pressure increased with papilloedema, usually after treatment; vertigo, headache

Eye disorders
Intraocular pressure increased, glaucoma, posterior sub capsular cataracts , Exophthalmoses

Cardiac disorders
Cardiac failure congestive
Reversible cardiac hypertrophy may occur in isolated cases in infants and small children treated over a prolonged period with high doses

Vascular disorders
Vasculitis necrotising, thromboembolism, hypertension

Gastrointestinal disorders

Pancreatitis, peptic ulcer with possible perforation and haemorrhage, oesophagitis ulcerative, abdominal distension

Skin and subcutaneous tissue disorders
Skin atrophy, petechiae and ecchymosis, erythema, hyperhidrosis, acne and skin hyper pigmentation

Musculoskeletal and connective tissue disorders
Aseptic necrosis of femoral and humeral heads, spinal compression fracture, muscle atrophy, myopathy , osteoporosis, muscular weakness, pathological fracture of long bones, tendon rupture

General disorders and administration site conditions
Hypersensitivity reactions 2), growth retardation, weight increased, impaired Healing

Investigations
Negative nitrogen balance due to protein catabolism, suppression of skin test reactions

1) Also see section 4.4 Special warnings and precautions for use
2) Also see 4.4. Special warnings and precautions for use and Table 1 Undesirable effects related to tetracosactide.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme by connecting to the following website: www.mhra.gov.uk/yellowcard.

4.9 Overdose
Overdosage is unlikely to be a problem when the product is used as a single dose for diagnostic purposes.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anterior pituitary lobe hormones and analogues – ACTH.

ATC code: H01AA02.

Tetracosactide acetate consists of the first 24 amino acids occurring in the ACTH sequence and displays the same physiological properties as ACTH. In the adrenal cortex, it stimulates the biosynthesis of glucocorticoids,

mineralocorticoids, and, to a lesser extent androgens. Prolonged use of Synacthen is reported to have minimal suppression of hypothalamic-pituitaryadrenal axis as compared to long-term corticosteroids.

The site of action of ACTH is the plasma membrane of the adrenocortical cells, where it binds to a specific receptor. The hormone-receptor complex activates adenylate cyclase, stimulating the production of cyclic AMP (adenosine monophosphate) and so promoting the synthesis of pregnenolone from cholesterol. From pregnenolone the various corticosteroids are produced via different enzymatic pathways.

5.2 Pharmacokinetic properties

Distribution
Tetracosactide is rapidly distributed and concentrated in the adrenals and kidneys, which lead to rapid decrease in its plasma levels.

There is no evidence of binding of ACTH to any particular plasma protein, though some non-specific interaction with albumin has been reported. Tetracosactide acetate has an apparent volume of distribution of approximately 0.4L/kg.

Biotransformation
In the serum, tetracosactide acetate is broken down by serum endopeptidases into inactive oligopeptides and then by aminopeptidases into free amino acids. The rapid elimination from plasma is probably not attributable to this relatively slow cleavage process, but rather to the rapid concentration of the active substance in the adrenal glands and kidneys.

Elimination
Following an intravenous injection, elimination of tetracosactide acetate from the plasma consists of 3 phases. The half-lives of these phases are approximately 7 minutes (0 to 1 hour), 37 minutes (1 to 2 hours) and 3 hours thereafter. Following an iv dose of ^{131}I-labelled tetracosactide acetate, 95 to 100% of the radioactivity is excreted in the urine within 24 hours.

5.3 Preclinical safety data
No studies have been performed to evaluate the mutagenic or carcinogenic potential of tetracosactide. No animal studies on fertility and reproduction toxicity have been performed with tetracosactide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Acetic acid,
Sodium acetate,
Sodium chloride,

Water for injection.

6.2 Incompatibilities
None known.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Synacthen should be protected from light and stored in a refrigerator (2 - 8°C).

6.5 Nature and contents of container
Synacthen Depot comes in cardboard boxes of 1 ampoule and 5 ampoules of 1 ml.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Mallinckrodt Specialty Pharmaceuticals Ireland Ltd
Sandyford Business Centre, Unit 7
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 43357/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
25 June 1998

10 DATE OF REVISION OF THE TEXT
08/06/2016

Appendix 4: Definitions of Adverse Events and Serious Adverse Events

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.

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.

Appendix 5: Classification of Adverse Events

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.

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.

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.

Appendix 6: Contact list of LEO, vendors, trial committees and coordinating investigators

Contact details for the clinical project manager (CPM), 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:

LEO Pharma A/S
Industriparken 55
DK-2750 Ballerup
Denmark

CRO(s)/vendors

Larix A/S, Lyskaer 8b, DK-2730 Herlev, Denmark will be responsible for all services related to electronic data capture and data management services, as agreed to in a Service Agreement/Contract.

ACM Global Laboratory, 23 Hospital Fields Road, York YO10 4DZ, United Kingdom or ACM Medical Laboratory, Inc., 160 Elmgrove Park, Rochester, New York 14624, USA will be responsible for all services related to the central laboratory analysis, as agreed to in a Service Agreement/Contract.

DSG, Inc, Great Valley Corporate Center, 325 Technology Drive, Malvern, Pennsylvania 19355, United States will be responsible for providing IWRS services as agreed to in a Service Agreement/Contract.

Klifo, Smedeland 36, 2600 Glostrup, Denmark will be responsible for drug storage, packaging, labeling, distribution and destruction of investigational medicinal product, as agreed to in the Service Agreement/Contract.

CRF Health, Brook House, 229-243 Shepherds Bush Road, Hammersmith, London, W6 7AN, United Kingdom will be responsible for all services related to ePRO and eDiary solutions, as agreed to in the Service Agreement/Contract.

Trial Committees

The Adjudication Panel:

Adjudicator	Expert role	Affiliation
PPD (PPD, MD)	Dermatologist	Texas Dermatology Associates, P.A. & Menter Cosmetic Institute, Dallas, Texas 75246, USA
PPD (PPD, MD)	Dermatologist	Sjællands Universitetshospital, 4000 Roskilde, Denmark
PPD (PPD, MD)	Endocrinologist	Odense University Hospital, 5000 Odense C, Denmark

Coordinating Investigators

International Coordinating Investigator: Dr. Mark Lebwohl

Appendix 7: EQ-5D-5L-PSO

Health Questionnaire

English version for the USA

(EQ-5D-5L + Psoriasis bolt on)

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN/DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY/DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

SKIN IRRITATION *(e.g. itching)*

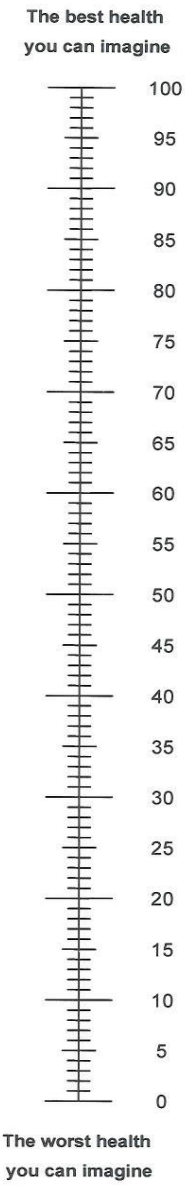
I have no itching ❑
I have slight itching ❑
I have moderate itching ❑
I have severe itching ❑
I have extreme itching ❑

SELF-CONFIDENCE

I have no problems with self-confidence ❑
I have slight problems with self-confidence ❑
I have moderate problems with self-confidence ❑
I have severe problems with self-confidence ❑
I have extreme problems with self-confidence ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 8: DLQI

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

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

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix 9: WPAI:PSO

Work Productivity and Activity Impairment: Psoriasis (WPAI:PSO)

The following questions ask about the effect of your psoriasis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past 7 days**, not including today.

2. During the past 7 days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your psoriasis. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past 7 days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past 7 days, how many hours did you actually work?

   _____ HOURS *(If "0", skip to question 6.)*

5. During the past 7 days, how much did your psoriasis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.

   Consider only how much psoriasis affected productivity while you were working.

   Psoriasis had no effect on my work — 0 1 2 3 4 5 6 7 8 9 10 — Psoriasis completely prevented me from working

   CIRCLE A NUMBER

6. During the past 7 days, how much did your psoriasis affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.

   Consider only how much psoriasis affected your ability to do your regular daily activities, other than work at a job.

   Psoriasis had no effect on my daily activities — 0 1 2 3 4 5 6 7 8 9 10 — Psoriasis completely prevented me from doing my daily activities

   CIRCLE A NUMBER

Appendix 10: Psoriasis Symptom Inventory (PSI) – 24 hours recall

Psoriasis Symptom Inventory (PSI)

For each of the following questions, please mark (☑) the box of the one answer that best describes your experience.

In the questions below, the phrase "*skin lesions*" refers to the areas of your skin affected by your psoriasis.

For the following group of questions, the "**last 24 hours**" means from right now - back to yesterday at this same time.	**Not at all**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1) Overall, during the last 24 hours, how severe was the **itch** from your psoriasis?					
2) Overall, during the last 24 hours, how severe was the **redness** of your skin lesions?					
3) Overall, during the last 24 hours, how severe was the **scaling** of your skin lesions?					
4) Overall, during the last 24 hours, how severe was the **burning** of your skin lesions?					
5) Overall, during the last 24 hours, how severe was the **stinging** of your skin lesions?					
6) Overall, during the last 24 hours, how severe was the **cracking** of your skin lesions?					
7) Overall, during the last 24 hours, how severe was the **flaking** of your skin lesions?					
8) Overall, during the last 24 hours, how severe was the **pain** you felt from your skin lesions?					

Appendix 11: Psoriasis Symptom Inventory (PSI) – 7 days recall

Psoriasis Symptom Inventory (PSI)

For each of the following questions, please mark (☑) the box of the one answer that best describes your experience.

In the questions below, the phrase "*skin lesions*" refers to the areas of your skin affected by your psoriasis.

For the following group of questions, the "**last 7 days**" includes today and the previous 6 days.	**Not at all**	**Mild**	**Moderate**	**Severe**	**Very Severe**
1) Overall, during the last 7 days, how severe was the **itch** from your psoriasis?					
2) Overall, during the last 7 days, how severe was the **redness** of your skin lesions?					
3) Overall, during the last 7 days, how severe was the **scaling** of your skin lesions?					
4) Overall, during the last 7 days, how severe was the **burning** of your skin lesions?					
5) Overall, during the last 7 days, how severe was the **stinging** of your skin lesions?					
6) Overall, during the last 7 days, how severe was the **cracking** of your skin lesions?					
7) Overall, during the last 7 days, how severe was the **flaking** of your skin lesions?					
8) Overall, during the last 7 days, how severe was the **pain** you felt from your skin lesions?					

Appendix 12: Protocol amendment history

The Protocol amendment summary of changes table for the current amendment is located directly before the table of contents.

Amendment 5 (22-Aug-2017)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The protocol was updated to include an additional country (Poland).

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Protocol section number	Description of change	Brief rationale
Section 6.1.1	Introduction of an additional country (Poland)	To increase the number of subjects participating in the ACTH challenge part of the trial.
Sections 10.9, 10.9.1.1, and 10.9.1.5 Table 1	Sponsor to provide Synacthen® to Polish sites for ACTH challenge.	Synacthen® is not registered in Poland.
Sections 6.1.3 and 10.2	Clarification that the first dose of investigational product may be applied at home.	To clarify that the first IP dose may be taken at home.
Section 8.12.2	Clinically significant out-of-range values of urine calcium and urine creatinine to be reported as adverse events only apply to the urine calcium/creatinine ratio, not to the individual values.	Urine calcium and urine creatinine values depend on the subject's hydration status.

Note that the changes in this amendment have also been described in an errata sheet (eTMF no. 000031211).

Amendment 4 (05-Jul-2017)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The protocol was updated to meet FDA advice received after their review of the protocol.

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Protocol section number	Description of change	Brief rationale
Section 8.1 Table 4	A physical examination has been added at Visit 2 for subjects who are not eligible for randomisation. Subjects attending Visit 2 have been treated with open-label IP for 4 weeks and should therefore have a physical examination done before leaving the trial.	To meet FDA advice.
Sections 6.1.1, 6.2 and 11.1	Due to difficulties in recruiting the required number of subjects into the HPA-axis part of the trial, the trial will remain open at selected sites for inclusion of subjects to participate in the HPA-axis part after completing recruitment of subjects into the main trial. The planned date of Last Subject Last Visit has been updated to reflect this.	To clarify that more than 380 subjects may be recruited to ensure 30 subjects in HPA-axis substudy.
Table 4	Clarification that screening visit and Visit 1 (baseline) may be performed on the same day if washout is not required.	Clarification of protocol text.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Note that the changes in this amendment have also been described in an errata sheet (eTMF no. 000025375).

Amendment 3 (14-Dec-2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The protocol was updated to describe a new treatment principle for non-active lesions during relapse treatment.

Note: The table below describes the main changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Protocol section number	Description of change	Brief rationale
Sections 3.3.2, 3.3.3, 6.1.1, 6.1.4, 6.1.4.1, 6.1.4.2, 6.1.4.3, 10.2, 10.4, and 11 Figure 1, Figure 2, Figure 3, and Figure 4, Table 3	In the previous version of the protocol it was specified that during relapse treatment, all psoriasis areas were to be treated with rescue medication (active LEO 90100) once daily for up to 4 weeks. This amendment introduces a new treatment principle so that only active areas will be treated with rescue medication for 4 weeks (regardless of whether the psoriasis clears before 4 weeks) while non-active psoriasis areas will continue twice weekly maintenance treatment.	To change the way psoriasis relapses are treated in order to better reflect how LEO 90100 will be used in real life.
Sections 3.3.3 and 10.2	Use of trial medication is now disallowed on the scalp during once-daily treatment periods (initial open-label treatment period and relapse treatment periods).	On request from the French regulatory authority (ANSM).
Sections 3.3.3, 6.1.4, 6.1.4.2, 6.1.5, 9.1, 9.5, and 16.2 Figure 1, Figure 2, Figure 3, and Figure 4 Table 2	An 8-week follow-up period has been added for all subjects after end of the maintenance period (or early withdrawal during maintenance) to capture if subjects develop rebound after twice weekly maintenance treatment.	On request from the French regulatory authority (ANSM).

Protocol section number	Description of change	Brief rationale
Sections 3.3.3, 9.3.6, 9.5, 11.3.6.2, and 16.2 Table 2	The definition of "rebound" has been updated to make it more clear when the observational period for rebound starts.	Clarification of protocol text.
Table 1	Specification that use of mild topical corticosteroids on the scalp is allowed during the trial.	Specification that mild topical corticosteroids may be used on the scalp.
Sections 3.3.3, 6.6.1, 6.1.4, 6.1.4.1, 6.1.4.2, 6.1.4.3, 10.2, and 10.4 Table 3	Terminology for the IP has been changed as follows: the term "LEO 90100" will be used for the IP used during the initial open-label phase, "maintenance IP" for the double-blinded IP used during maintenance treatment, and "rescue IP" for open-label IP used during relapse treatment.	Clarification of terminology used for the IP.
Sections 11.3.3.3, 11.3.3.5, 11.3.3.6,11.3.4.3, 11.3.4.4, and 11.3.8	HPA axis testing has been removed as a stratification factor in the statistical analyses.	The HPA axis test is a safety parameter which is only obtained for a subset of subjects.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Note that the changes in this amendment have also been described in an errata sheet (eTMF no. 00645283).

Amendment 2 (07-Sep-2016)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the trial.

Overall rationale for the amendment

The protocol was updated to allow dermatological assessments to be performed by qualified staff who are not dermatologists.

Note: The table below describes the main changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in **bold** and deleted text has ~~a line through it~~).

Protocol section number	Description of change	Brief rationale
Section 7.2	Removal of inclusion criterion #3: ~~3.Attending a hospital out-patient clinic, the private practice of a qualified, experienced dermatologist, or the practice of a general practitioner experienced in the treatment of psoriasis vulgaris patients~~	Inclusion criterion not needed as certified physician's assistants and advanced registered nurse practitioners may now perform dermatological assessments.
Sections 8.11 and 8.16	Certified physician's assistants and advanced registered nurse practitioners are allowed to perform dermatological assessments.	The dermatology assessments in this protocol can be performed as reliably by qualified staff that are not dermatologists.
Section 10.1	The IP description tables (LEO 90100 and foam vehicle) were updated to reflect that LEO releases the final IP.	Correction of error.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Note that the changes in this amendment have also been described in an errata sheet (eTMF no. 00622834).

Amendment 1 (19-Aug-2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The protocol was updated to implement advice from the FDA and the Danish Medicines Agency (DMA).

Note: The table below describes the changes in each section. Changes have either been summarised (written with plain text only) or marked as tracked changes (text added to the protocol is written in *italics* and deleted text has a ~~line through it~~).

Protocol section number	Description of change	Brief rationale
Section 7.2	Change of inclusion criteria #3 and #12: 3. Attending a hospital out-patient clinic ~~or~~, the private practice of a qualified, experienced dermatologist, *or the practice of a general practitioner experienced in the treatment of psoriasis vulgaris patients* ~~12. Access to the internet (e.g. computer, tablet or smartphone) and able to complete online questionnaires about health status~~ *12. Signed and dated informed consent obtained for having ACTH challenge tests performed*	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 7.3	Addition of exclusion criteria # 22 and #23 and change of exclusion criterion #25: *22. Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a contract research organisation (CRO) involved in the trial* *23. Subjects who are institutionalised by court order or by local authority.* 25. Known or suspected hypersensitivity to component(s) of CORTROSYN® (including cosyntropin/tetracosactide) *(in the US) / Synacthen® (including tetracosactide) (in Europe)*	The protocol has been updated several places due to input received from internal and external stakeholders.

Protocol section number	Description of change	Brief rationale
Sections 3.3.3, 6.1.1, 6.1.3, 7.9, 10.2, 10.6, 11 and 11.1	The criterion for entering the maintenance phase of the trial has been changed from "a PGA score of clear or almost clear" to "a PGA score of clear or almost clear with at least a 2-step improvement". Due to this change, it is expected that more subjects will have to leave the trial after the open-label phase. Consequently, the number of subjects to be enrolled has been increased from 752 to 832.	To meet FDA advice.
Sections 6.1.4, 6.1.4.1, 6.1.4.2, and 10.2	Clarification that during maintenance phase, subjects will be instructed to continue applying the IP to areas on the trunk and limbs where lesions have cleared after initiation of treatment at baseline. Subjects will also be instructed to treat any new psoriatic lesions. Following confirmation of a relapse, subjects will be instructed to apply IP on the affected areas (all active psoriatic lesions as well as to areas where lesions had cleared after initiation of treatment at baseline) once daily for up to 4 weeks.	To meet FDA advice.
Section 8.1	A physical examination at the end of treatment and in case of early withdrawal has been added.	To meet FDA advice.
Sections 3.3.3, 8.1, 8.12.3.1, 8.12.4, Table 8	Assessment of vital signs in case of early withdrawal has been added. ACTH challenge test and sampling of biomarkers at Week 28 have been added and the total blood sampling volume to be drawn has been updated.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 3.3.3, 6.2, 8.12.1, and 16.1	The number of subjects to be randomised for the HPA assessment has been increased from 25 to 30 subjects. Furthermore, it has been added that HPA axis assessment will also be performed at Week 28 and in case of early withdrawal.	To meet DMA advice.
Section 11.3.4.4	Time to first relapse according to m-PASI has been added as an exploratory endpoint to be able to make an indirect comparison to other studies where this definition is used.	To meet DMA advice.

Protocol section number	**Description of change**	**Brief rationale**
Section 11.3.3.3	Update of the primary endpoint: The primary endpoint, *is* time to first relapse during the maintenance ~~period,~~ *phase, where relapse is an exacerbation of psoriasis defined as a PGA of at least 'mild'. This* will be calculated as the number of days from randomisation to the day where the subject has the first relapse confirmed. For subjects who either do not encounter a relapse or are withdrawn from the trial, the number of days will be treated as a censored observation at the day of end of trial visit.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 10.6, 11.3.3.5, 11.3.3.6, and 11.3.4.3	Specification that randomisation will also be stratified by HPA axis testing; HPA axis testing at baseline has been included as factor in the statistical analysis model.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 11.3.5, 11.3.5.1, 11.3.5.2, 11.3.5.3, 11.3.5.4, 11.3.5.5, and 13.2	Clarification of statistical analyses and data handling of PROs.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 11.3.6.3 and 11.3.6.6	Statistical analyses of local safety and tolerability and clinical safety laboratory evaluations have been specified further.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 12.1	The following data have been added to the list of data to be provided to the adjudication committee: (i) the investigator's assessments of causal relationship of long-term use of corticosteroids to the event and (ii) information on the action taken with IP.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 10.6.1	Clarification of how to handle the randomisation files.	The protocol has been updated several places due to input received from internal and external stakeholders.

Protocol section number	Description of change	Brief rationale
Section 10.7.3 Table 8.1	Additional visits have been added for recording of treatment compliance.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 7.3, 8.1, 8.12.1, and 10.9, 10.9.1.2, 10.9.1.3, 10.9.1.4, Table 15 Appendix 3	French sites have been included in the HPA axis testing and Synacthen® has therefore been added for ACTH challenge in Europe.	French site have been added.
Table 1	Vitamin D supplements > 400 IU/day have been added as prohibited medication.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 7.8.2	Specification that inhaled steroids are disallowed during the last 4 weeks prior to ACTH-challenge.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 7.8.2	In case of use of sunscreen, it has been specified that an interval of at least 1 hour is recommended between applications.	The protocol has been updated several places due to input received from internal and external stakeholders.
Table 3	For permitted concomitant anti-psoriatic treatment, it has been added that emollient should not contain alpha-hydroxy acids, beta-hydroxy acids, or acetylic acid; emollients containing urea acid (≤ 5%) are allowed.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 8.11 and 8.16	Specification that all physician's dermatological assessments of the treatment area must be performed by a dermatologist or general practitioner experienced in treating psoriasis vulgaris (also added as an inclusion criterion; see above).	The protocol has been updated several places due to input received from internal and external stakeholders.

Protocol section number	Description of change	Brief rationale
Section 8.12.1	Specification that in case a patient discontinues the trial prior to Week 56, a follow-up visit has to be scheduled within 7 days of the last treatment period visit for the purpose of performing the ACTH challenge test, if the test has been not performed on the same day.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 3.3.3, 8.1, and 8.13.3	Specification that WPAI:PSO will be assessed only at Week 28 and Week 56 or at the last treatment visit.	The protocol has been updated several places due to input received from internal and external stakeholders.
Sections 3.3.3, 8.1, and 8.12.1	Specification that subjects are requested to give a separate written consent for having ACTH challenge tests performed.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 9.1	Clarification that abnormal findings at screening should be recorded as diagnoses in the Concomitant Medication page if medication is currently being taken for the condition. If not, the diagnosis should be documented as medical history in the eCRF.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 9.1.1	Clarification of when applications site reactions should be reported as AEs.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 9.1.2	Clarification of the requirements for reporting of AEs of concern associated with long-term topical corticosteroid use.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 9.3.2	Definition of overdose has been added.	The protocol has been updated several places due to input received from internal and external stakeholders.

Protocol section number	**Description of change**	**Brief rationale**
Sections 9.3.2 and 11.3.6.2	Specification that relapse of psoriasis during the maintenance phase of the trial is not to be reported as an AE. A definition of rebound effect has been added.	The protocol has been updated several places due to input received from internal and external stakeholders.
Section 10.5	Further instructions on storage requirements of the IPs have been added.	The protocol has been updated several places due to input received from internal and external stakeholders.
Throughout	Minor editorial and document formatting revisions.	Minor, have therefore not been summarised.

Note that the changes in this amendment have also been described in an errata sheet (eTMF no. 00626924).

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Reason for signing: Approved	Manage Approver Verdict(s) Name: PPD Capaci Date of signature: 12-Apr-2018 13:04:59 GMT+0000

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