Statistical Analysis Plan

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

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

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

LEO Pharma A/S	**Trial ID:**	**LP0076-1017**
	Date:	**16-Mar-2018**
	Version:	**1.0**

1 Statistical Analysis Plan Approval

1.1 Approval Statement

On behalf of LEO, the Biostatistics Lead and the Medical Lead, are authorised to approve the Statistical Analysis Plan.

The QC statistician has by approving this document confirmed that the statistical information has been subject to statistical quality control.

The following persons have approved this Statistical Analysis Plan using electronic signatures as presented on the last page of this document.

PPD

Biostatistics Lead, Global Clinical Operations

PPD

Medical Lead, Medical Sciences and Safety

PPD

QC Statistician, Biostata Aps

2 Statistical Analysis Plan Statements

2.1 Compliance with Good Clinical Practice

This Statistical Analysis Plan is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3: Structure and Content of Clinical Study Reports, E6: Good Clinical Practice, and E9: Statistical Principles for Clinical Trials).

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3 List of Abbreviations

3.1 List of Abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
CRF	Case Report Form
CTR	Clinical Trial Report
ICH	International Conference on Harmonisation
IGA	Investigator's global assessment
LOCF	Last Observation Carried Forward
LLOQ	Lower Limit of Quantification
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
SAP	Statistical Analysis Plan

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5 Introduction

The statistical analysis will be performed as outlined in the Consolidated Clinical Study Protocol. This Statistical Analysis Plan, prepared after review of the data, contains a more technical and detailed elaboration of some points in the statistical analysis described in the

protocol. Minor deviations from the planned data presentation and analysis are accounted for. The analysis sets which are to be used for the statistical analysis are presented in Analysis Set Definition Document.

Table 1 includes protocol amendments that are relevant to the statistical reporting. The inclusion criteria for subjects *not* performed HPA and PK assessments has been updated in Consolidated Clinical Study Protocol, version 4.0, dated 16-Feb-2015. The extent of psoriasis required on the body and the severity of psoriasis required on the body and the scalp has been revised to better reflect psoriasis commonly seen in the adolescent population. The definition of 'controlled disease' under the secondary response criteria was updated accordingly. More details can be found in LP0076-1017 Summary of Amendment(s) to a Clinical Trial Authorisation, 02-Mar-2015 (v1.0).

Table 1: Protocol amendments that are relevant to the statistical reporting.

Section no in Consolidated Clinical Study Protocol version 4.0 and 6.0	To	From :
10.4.1.3 (a and b, BODY) The inclusion criteria for subjects *not* performing HPA and PK assessments was updated.	At SV2 and Visit 1, a clinical diagnosis of body (trunk and/or limbs) psoriasis which is: a. *more than or equal to **3% of the body surface area** (excluding psoriatic lesions of the face and sensitive areas), and* b. of at least ***mild*** severity according to the investigator's global assessment of disease severity on the body. *At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:* *a. more than or equal to 10% of the scalp area, and* *b. of at least mild severity according to the investigator's global assessment of disease severity on the scalp*	At SV2 and Visit 1, a clinical diagnosis of scalp and body (trunk and/or limbs) psoriasis which is: a. of an extent of ***10 to 35% of the body surface area*** (excluding psoriatic lesions of the face and sensitive areas. Sensitive areas include armpits, groin, under the breasts and in other skin folds around the genitals and buttocks), and b. of at least ***moderate*** severity according to the investigator's global assessment of disease severity on the body.

10.4.1.3 (a and b, SCALP) The inclusion criteria for subjects *not* performing HPA and PK assessments was updated.	*At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is:* *a*. more than or equal to 10% of the scalp area, and *b. of at* ***least mild*** *severity according to the investigator's global assessment of disease severity on the scalp*	At SV2 and Visit 1, a clinical diagnosis of scalp psoriasis which is: a. more than or equal to 10% of the scalp area, and b. of at least ***moderate*** severity according to the investigator's global assessment of disease severity on the scalp.
10.10.1 Revised secondary response criteria.	Subjects with "Controlled disease" (i.e., "Clear" or "Almost clear***" for subjects with at least "Moderate" disease at baseline, "Clear" for subjects with "Mild" disease at baseline)*** according to the investigator's global assessment of disease severity on the body at end of treatment.	Subjects with "Controlled disease" (i.e., "Clear" or "Almost clear") according to the investigator's global assessment of disease severity on the body at end of treatment.

6 Statistical Analysis

The statistical analysis will be carried out as described in the Consolidated Clinical Study Protocol with a few exceptions as described below.

Lists of planned tables, figures and individual subject data listings for the Clinical Trial Report are provided in Appendix 1.

6.1 Baseline Considerations

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

Age and sex will be presented by country and not by centre as described in the protocol, due to too few number of subjects at most centres.

The age will be presented in three categories:

- Overall
- 12 to 14 years
- 15 to <17 years.

A table of serum cortisol concentrations at time 0, and at 30 and 60 min after ACTH challenge at baseline, although not planned in the protocol, will be produced for the per protocol analysis set.

Any abnormalities recorded during physical examination will be included in concurrent diagnoses table.

The baseline is defined as last assessment performed prior the first application of IMP.

6.1.1 Compliance

As described in the protocol, compliance with treatment instructions will be tabulated for all subjects who applied any IMP. Compliance with treatment instructions will be presented for all subjects in the safety analysis set and per protocol analysis set. Compliance is defined by number of missed days due to other reasons than cleared psoriasis in relation to treatment period. Treatment period is defined as the number of days from the treatment assignment at Visit 1 to either trial completion or early withdrawal.

The number and percentage of subjects who either did or did not comply with the trial treatment regimen will be summarized. The extent of non-compliance as categories of the percentage of applications missed will also be presented:

- No
- Yes: <=10% applications missed
- Yes: >10% to <=20% applications missed
- Yes: >20% to <=30% applications missed
- Yes: >30% to <=40% applications missed
- Yes: >40% to <=50% applications missed
- Yes: >50% applications missed
- Total

6.2 Analysis of Efficacy

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

'Controlled disease' will be presented in a table by age group, the categories to be used are the same as defined in section 6.1.

Additional tables, not planned in the protocol, will be produced:

- Controlled disease (IGA on the body) at end of treatment by race
- Controlled disease (IGA on the body) at end of treatment by baseline total extent of psoriasis

Baseline for the efficacy is defined as last observation collected prior the first application of IMP, and is defined as Visit 1 for all assessments.

6.3 Analysis of Safety

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

Baseline for the safety analysis is defined as last observation collected prior the first application of IMP, which is Screening Visit 2.

6.4 ACTH-Challenge

The results from the ACTH-challenge will be presented as described in the protocol for the per protocol analysis set.

According to the ACTH-challenge procedure described in the protocol, samples of venous blood were to drawn exactly 30 min and 60 min after the CORTROSYN®/SYNACTHIEN® injection, however a time deviation of +/- 10 minutes is considered acceptable as the overall value of the test is to observe substantial increases in cortisol levels and identify adrenal insufficiency up to 1 hour after the initial injection, therefore the exact timing of the incremental time points (30 and 60 minutes) is of less importance. Samples outside the acceptable deviation will not be included in the analysis. No measurements outside the acceptable deviation were observed.

6.4.1 Exposure

As described in the protocol, the duration of exposure (weeks) and extent of exposure (subject-treatment-weeks) to LEO 80185 will be summarized for the safety analysis set.

6.4.2 Drug Accountability

The amount of IMP used in grams and the average weekly amount used in grams will be tabulated for the safety analysis set, and separately for three different treatment periods (first four weeks, second four weeks, and the total treatment period).

The average weekly amount of IMP used, during the total treatment period, in defined usage categories, will be tabulated; this table was not planned in the protocol:

- <20 g/week
- 20 to <40 g/week
- >=60 g/week
- Total

The mean weight of full bottles, including label of IMP, is presented in Table 1 for each batch and kit number. Also the label type is given.

Table 2: Mean weight of full bottles of IMP by batch number and kit number

Batch number	Kit number	Weight of a full bottle + label (g)	Label Type
131537101	0001 - 3200	86.8 g	Booklet
P14090	3201 - 4757	86.9 g	Booklet
P14090	4758 - 5600	86.6 g	Single panel
P14090	5797-5955	87.0 g	Single panel

For each treatment period the following rules for calculating amount of IMP used will apply.

For each subject the weight of IMP used for a particular treatment period will be determined by calculating the difference between the weight of a set of full bottles dispensed and the weight of the returned bottles.

If any subjects received bottles for a particular treatment period but did not return them all, then the amount of IMP used for that treatment period will not be calculated. If any bottles are

not dispensed, they will not contribute to the weight of IMP used for that treatment period. If any bottles are returned with their seal unbroken, the weight of IMP used from that bottle will be assigned a value of zero. If a returned bottle weighs more than the estimated mean weight of a full bottle, it will be assumed that zero grams were used.

The average weekly amount of IMP used will be calculated for each subject as the amount of IMP used for a particular treatment period, divided by the duration (days) of the treatment period and then multiplied by 7.

6.4.3 Adverse Events

The AEs will be presented for the safety analysis set as described in the protocol.

The AEs are coded in accordance with the MedDRA dictionary version 15.1.

The number of events will be presented in all adverse events tables where number of subjects is presented.

One subject had a serious adverse event and one subject was withdrawn early from the trial due to an adverse event, therefore serious adverse events and adverse events leading to withdrawal will not be tabulated, but will be evaluated separately in the report.

Additional tables, not planned in the protocol will be produced:

- Adverse events by age group, MedDRA, primary system organ class and preferred term
- Adverse events by sex, MedDRA primary system organ class and preferred term
- Adverse events by race, MedDRA primary system organ class and preferred term
- Adverse events by baseline IGA on the body, MedDRA primary system organ class and preferred term
- Adverse events by baseline total extent of psoriasis, MedDRA primary system organ class and preferred term
- Adverse events by IMP usage (<40 g/week, ≥40 g/week), MedDRA primary system organ class and preferred term.

Adverse events will be presented separately for subjects using at least 40 g per week of IMP during the total treatment period and for those using less than 40 g per week of IMP during the total treatment period.

6.4.4 Laboratory Data

The laboratory data will be presented for the safety analysis set as described in the protocol.

However, 25-hydroxy vitamin D baseline values will not be summarized since no abnormal values have been observed.

The following approach will be used in case of repeated or missed laboratory measurements:

- if an initial measurement was normal but the measurement was still repeated then the initial measurement will be presented in the tables and both measurements will be included in the listing.
- if an initial measurement was repeated by mistake then the initial measurement will be presented in the tables and both measurements will be included in the listing.
- if an initial measurement was abnormal and the measurement was repeated due to a technical problem then the repeated measurement will be presented in the tables and both measurements will be included in the listing.
- if an initial measurement was missing but a measurement from an unscheduled visit is available and the unscheduled visit was performed within 5 days after the actual visit then the measurement from the unscheduled visit will be used, for example one measurement from an unscheduled visit after Visit 3 will be included in the analysis of albumin corrected serum calcium (gives a total of 100 measurements).

The number of measurements outside the reference range will be presented in relevant laboratory tables. The number of measurements for other than primary and secondary endpoints that fall outside the limit for quantification will be presented in relevant laboratory tables.

6.4.5 Other observations

PK evaluation

As most plasma concentrations were below LLOQ the PK parameters will not be calculated at Week 4 for each assayed compound.

Plasma concentrations will be presented in the listing.

Vital signs

For systolic and diastolic blood pressure and heart rate, the absolute value by visit and change from baseline (SV2) to Week 4 (Visit 3) and Week 8 (Visit 5) will be summarized

Clinically significant abnormalities in the vital signs at baseline (SV2), Week 4 and/or Week 8 will not be presented since no clinically significant abnormalities were observed. Any abnormalities at Week 4 and/or Week 8 that were not present at baseline will be presented in the listing.

The following approach will be used in case of repeated vital signs measurements:

- if an initial measurement was normal but the measurement was still repeated then the initial measurement will be presented in the tables
- if an initial measurement was abnormal and the measurement was repeated then the average of both measurements will be presented in the tables.

All measurements will be included in the listings (initial measurement and repeated measurements).

6.5 General Principles

6.5.1 Pooling of Trial Sites

There will be no pooling of centres.

6.5.2 Handling of Drop-outs and Missing Values

The efficacy and laboratory data will be tabulated by visit using an observed cases approach except for the tabulation of end of treatment values for which the LOCF approach will be used.

The extent of missing values are described in

Table 3 for the primary endpoints and secondary endpoints involving laboratory measurements:

Table 3: Number of missing values and number of observations/Total.[1]

Endpoint	Test	Number of Missing Values (Number of observations/Total)		
		Screening Visit 2	Week 4	Week 8
Primary	Albumin corrected serum calcium	0 (107/107)	5 (99/104)	3 (87/90)
Primary	24-hours urinary calcium excretion	9 (98/107)	12 (92/104)	11 (79/90)
Primary	Serum Cortisol at time 0	0 (33/33)	1 (31/32)	1 (29/30)
Primary	Serum Cortisol at time 30 min[2]	0 (33/33)	1 (31/32)	1 (29/30)
Primary	Serum Cortisol at time 60 min[2]	0 (33/33)	1 (31/32)	1 (29/30)
Secondary	Urinary calcium:creatinine ratio	9 (98/107)	12 (92/104)	11 (79/90)
Secondary	Serum alkaline phosphatase	0 (107/107)	5 (99/104)	3 (87/90)

1: Duplicates by subject, visit and numerical results are excluded. The table includes only subjects assigned to treatment

2: Serum Cortiosol 30 min and 60 min after ACTH challenge

6.5.4 Treatment Labels

The treatment label to be used in text and tables in the CTR and in the individual subject data listings is ‘LEO 80185’.

Appendix I

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[Note: X% is 5% or smaller percentage]

Signature Page for TMF-000048500 v1.0

Reason for signing: Approved	Approver Verdict(s) Name: PPD Capacity: Biostatistics Date of signature: 16-Mar-2018 10:08:46 GMT+0000

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