Statistical Analysis Plan

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

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

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

LEO Pharma A/S	**Trial ID:**	**LP0053-1108**
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	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
BSA	Body Surface Area
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CRF	Case Report Form
CTR	Clinical Trial Report
FDLQI	Family's Dermatology Life Quality Index
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
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Classification

4 Statistical Analysis Plan Authors

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5 Introduction

The statistical analysis will be performed as outlined in the Consolidated Clinical Trial 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.

No protocol amendments that are relevant to the statistical reporting have been made.

6 Statistical Analysis

The statistical analysis will be carried out as described in the Consolidated Clinical Trial 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 assigned to treatment and separately for the per protocol analysis set.

Age, sex, ethnicity, race and baseline disease severity according to the PGA on the body and scalp will be given 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.

Tabulation of concomitant medication will be made for ACT Level 1 and ACT Level 4. The tabulation of the concurrent diagnoses will include SOC and PT, and will be made for Visit 1.

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 assigned to treatment. Non-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.

‘Treatment success’ according to PGA on the body at week 4 and at end of treatment will be presented in a table by age group. The categories to be used are the same as defined in section 6.1, however the overall group will not be presented.

‘Treatment success’ according to PGA on the body at week 4 and at end of treatment will be presented in a table by country and not by centre as described in the protocol.

The following additional tables, not planned in the protocol, will be produced:

- Treatment success (PGA on the body and scalp) at week 4 and end of treatment by baseline extent of body psoriasis and scalp psoriasis: full analysis set

The total extent of psoriasis will be presented in following three categories:

- 2-10%
- >10-15%
- >15-30%

The categories of the extent of body psoriasis and scalp psoriasis will be defined later.

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.

Treatment success is defined as PGA score of 'clear' or 'almost clear' for subjects with at least a 2-step improvement from baseline i.e.:

'clear' or 'almost clear' for subjects with at least 'moderate' disease at baseline and 'clear' for subjects with 'mild' disease at baseline.

Treatment success for subject's global assessment is defined as 'clear' or 'very mild'.

The CDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. For interpretation of incorrectly completed questionnaires following rules will be used:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If both question 7a and 7b are completed the higher of the two scores should be counted

The FDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. For interpretation of incorrectly completed questionnaires following rules will be used:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.

3. If two or more response options are ticked, the response option with the highest score should be recorded.
4. If there is a response between two tick boxes, the lower of the two score options should be recorded.

6.3 Analysis of Safety

The analysis of safety will be based on the safety analysis set, except where otherwise stated. The analysis of the results from the ACTH-challenge test will be based on the per protocol analysis set.

According to the ACTH-challenge procedure described in the protocol, samples of venous blood were to be drawn exactly 30 min and 60 min after the CORTROSYN®/Synacthen ® 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 window will not be included in the analysis. No measurements outside the accepted window were observed.

The tabulation of following two analyses will not be made due to too few number of subjects:

- serum cortisol concentration at time 0 and at 30 and 60 minutes after ACTH challenge for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge
- change in serum cortisol concentration from time 0 to 30 and 60 minutes at baseline, week 4 and FU2 for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge

Instead the tabulation of individual data for subjects with serum cortisol concentration <=18 mcg/dL at either 30 minutes or 60 minutes after ACTH challenge will be presented.

Baseline for the safety analysis is defined as last observation collected prior the first application of IMP.

6.3.1 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 per protocol analysis set, and separately for three

different treatment periods (first two weeks, second two weeks, and the total treatment period).

Furthermore, a plot of the average weekly amount of IMP use over the total treatment period against baseline extent of the total BSA involvement will be presented for the safety analysis set and the per protocol analysis set.

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
- 40 to <50 g/week
- 50 to <60 g/week
- >=60 g/week
- Total

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

Table 1: Mean weight of full cans of IMP by batch number and kit number

Batch number	Kit number	Weight of a full bottle + label (g)	Label Type
CCI	CCI - CCI	CCI	Single panel
CCI	CCI - CCI	CCI	Booklet
CCI	CCI - CCI	CCI	Booklet
CCI	CCI - CCI	CCI	Single panel
CCI	CCI - CCI	CCI	Booklet

For each treatment period the following rules for calculating the 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 cans dispensed and the weight of the returned cans.

If any subject received cans 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 cans are not dispensed, they will not contribute to the weight of IMP used for that treatment period. If any cans 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.

6.3.2 Exposure

As described in the protocol, the duration of exposure (weeks) and extent of exposure (subject-treatment-weeks) to LEO 90100 will be summarized for the safety analysis set.

6.3.3 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 18.0.

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

No subjects had any serious adverse events and no 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.

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 PGA on the body, MedDRA primary system organ class and preferred term
- Adverse events by baseline PGA on the scalp, MedDRA primary system organ class and preferred term

- Adverse events by baseline total extent of body psoriasis, MedDRA primary system organ class and preferred term
- Adverse events by baseline total extent of scalp psoriasis, MedDRA primary system organ class and preferred term
- Adverse events by IMP usage, MedDRA primary system organ class and preferred term.

Adverse events will be presented separately for two categories of IMP usage, the categories will be defined later.

Following table will only be made for the subgroups 12 to 14 years and 15 to <17 years:

- Adverse events by age group, MedDRA primary system organ class and preferred term

6.3.4 Clinical Laboratory Evaluation

The laboratory data will be presented for the safety analysis set, except where otherwise stated.

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.

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.

The measurements below limit of quantification for primary or secondary endpoints will replaced by the limit of quantification.

6.3.5 Other observations

PK evaluation

The PK evaluation will be presented in a bioanalytical report.

Plasma concentrations will be presented in the listing.

Vital signs

For systolic and diastolic blood pressure, heart rate and temperature, the absolute value by visit and change from baseline to each visit will be summarized

Clinically significant abnormalities in the vital signs at baseline and Week 4 will be presented. Any abnormalities at Week 4 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).

Baseline for vital signs is defined as last observation collected prior the first application of IMP (visit 1 and not screening visit 2 as written in the protocol).

Local Safety and Tolerability

Local safety and tolerability will be tabulated as described in the protocol.

6.4 General Principles

6.4.1 Pooling of Trial Sites

There will be no pooling of centres.

6.4.2 Handling of Drop-outs and Missing Values

An observed cases approach will be used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit), except for the tabulation of end of treatment. The end of treatment value for a particular parameter will be defined as the last value recorded for that parameter up to and including Visit 3 (Week 4). However, for laboratory parameters this will be the last value recorded after baseline (SV2) up to and including Visit 3.

The extent of missing values are described in Table 2 for some of the primary endpoints and secondary endpoints involving laboratory measurements:

Table 2: Number of observations/Total.[A]

		(Number of observations/Total)	
Endpoint	Test	Screening Visit 2	Week 4
Primary	Albumin corrected serum calcium[B]	104/106	102/103
Primary	24-hours urinary calcium excretion[C]	33/34	33/33
Primary	24-hours urinary calcium:creatinine ratio[C]	32/34	31/33
Primary	Serum cortisol at time 0[D]	33/33	33/33
Primary	Serum cortisol at time 30 min[D]	33/33	33/33
Primary	Serum cortisol at time 60 min[D]	33/33	33/33
Secondary	Urinary calcium:creatinine ratio in spot urine[E]	58/72	58/70

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

B: All subjects assigned to treatment.

C: Only for 24-hour urine HPA subjects.

D: Only for the per protocol analysis. Serum Cortisol at time 0 and 30 min and 60 min after ACTH challenge.

E: Only for spot urine non-HPA subjects.

6.4.3 Treatment Labels

The treatment label to be used in text and tables in the CTR and in the individual subject data listings is ‘LEO 90100’.

Appendix I

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Note: Calculate 95% CI based on a binomial distribution for the proportion of subjects with 'treatment success' at week 4 and end of treatment.

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Note: Only for subjects with baseline score ≥5.

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Table 3-73 Change in temperature rate from baseline to each visit: safety analysis set

Figures

Figure 3-1 Average weekly amount of IMP used over the total treatment period against change from baseline to Week 4 in albumin corrected serum calcium: safety analysis set.

Figure 3-2 Average weekly amount of IMP used over the total treatment period against change from baseline to end of treatment in albumin corrected serum calcium: safety analysis set.

Figure 3-3 Average weekly amount of IMP used over the total treatment period against baseline extent of total BSA involvement: safety analysis set and per protocol analysis set.

Patient Data Listings (Appendix 1)

1-7: Subjects Receiving Investigational Product from Specific Batches

Patient Data Listings (Appendix 2)

Appendix 2.1: Discontinued Subjects

Listing 1-1: Screening failures

Listing 1-2: Reasons for withdrawal from trial

Appendix 2.2: Protocol Deviations

Listing 2-1: Protocol deviations

Listing 2-2: Comments from CRF

Appendix 2.3: Trial Analysis Sets

Listing 3-1: Trial Analysis Sets

Listing 3-2: Reasons for Exclusions from Analysis Sets

Appendix 2.4: Demographic Data

Listing 4-1: Demographics

Listing 4-2: Duration of Psoriasis Vulgaris

Listing 4-3: Actual Trial Period

Listing 4-4: Medical History

Listing 4-5: Concomitant Diagnoses at Baseline

Listing 4-6: Concomitant Medication

Appendix 2.5: Compliance and/or Investigational Product Concentration Data

Listing 5-1: Compliance

Listing 5-2: Drug Accountability

Listing 5-3: Exposure Dates

Appendix 2.6: Efficacy Data

Listing 6-1: Physician's Global Assessment of Disease Severity

Listing 6-2: Physician's Assessment of Extent of Psoriasis

Listing 6-3: Physician's Assessment of Extent and Severity of Clinical Signs and PASI Score

Listing 6-4: Subject's Global Assessment of Disease Severity

Listing 6-5: Subject's Assessment of Itch

Listing 6-6: Subject's Assessment of Itch-Related Sleep Loss

Listing 6-7: Children's Dermatology Life Quality Index.

Listing 6-8: The Family Dermatology Life Quality Index

Appendix 2.7: Safety Data

Listing 7-1 Deaths

Listing 7-2 Serious Adverse Events

Listing 7-3 Subjects Withdrawn due to AE

Listing 7-4 Severe Adverse Events

Listing 7-5 Adverse Events

Listing 7-6 Dietary Calcium Intake

Listing 7-7 Albumin-Corrected Serum Calcium

Appendix 2.8: Listing of Laboratory Values by Subject

Listing 8-1 Physical Examination

Listing 8-2: Laboratory Measurements

Listing 8-3: Abnormal Laboratory Measurements

Listing 8-4: ACTH Challenge Test

Listing 8-5: Vital signs

Listing 8-6 PK Measurements

Additional Tables for Results Reporting in Clinical Trial Data Registries

Table 4-1 Age group: subjects assigned to treatment

Table 4-2 Non-serious AEs occurring in ≥[X]% subjects by MedDRA primary SOC and preferred term: safety analysis set
[Note: X% is 5% or smaller percentage]

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