Cover Page

**Official title:** A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel group, open trial of LEO 90100 foam versus Dovobet® ointment
**LEO Pharma number:** LP0053-1422
**NCT number:** NCT03806790
**Date:** 21-Jun-2019

# Statistical Analysis Plan

# Efficacy and safety of LEO 90100 foam in Japanese subjects with psoriasis vulgaris

Phase 3

A phase 3, national, multi-centre, 4-week, prospective, randomised, controlled, parallel-group, open trial of LEO 90100 foam versus Dovobet® ointment

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|---|---|---|
| **LEO Pharma A/S** | **Trial ID:** | **LP0053-1422** |
| | **Date:** | **21JUN2019** |
| | **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 Science and Safety

PPD

QC Statistician, Biostatistics

# 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).

# Table of Contents

# 3 List of Abbreviations

## 3.1 List of Abbreviations

| | |
|---|---|
| ATC | Anatomical Therapeutic Chemical |
| CPMP | Committee for Proprietary Medicinal Products |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CRO | Contract Research Organisation |
| CTP | Clinical Trial Protocol |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| LOCF | Last observation carried forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PPAS | Per protocol analysis set |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |

# 4 Statistical Analysis Plan Authors

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# 5 Introduction

The statistical analysis will be performed as outlined in the Clinical Trial Protocol (CTP). This Statistical Analysis Plan, prepared before the end of the blinding period, contains a more technical and detailed elaboration of some points in the statistical analysis described in the CTP. Refer to the "Blinding Plan" as referenced in eTMF, document number TMF-000130194, for the blinding period. In addition, any changes to the analyses planned in the CTP are described.

# 6 Statistical Analysis

## 6.1 Software and Dictionaries

The software and its versions used in this trial are listed below.

| | Software and Versions |
|---|---|
| Operating System | Microsoft Windows 7 |
| Statistical Analysis Software | SAS Ver.9.3 or later |
| Tabulation Software | Microsoft Word 2010 |

The coding items and dictionaries used in this trial are listed below.

| Category | Dictionary | Remarks |
|---|---|---|
| Adverse Event,<br>Concurrent Diagnoses<br>Indications for concurrent medications<br>Concurrent procedures and their indications | MedDRA*/J Version 21.1 | Apply System Organ Class (SOC) and Preferred Term (PT) to Items listed opposite |
| Product Name (Concurrent Medication) | WHO Drug Version Sep 2018 | |

## 6.2 Protocol Deviations

Protocol deviations for all subjects will be presented in the listings.

## 6.3 Subject Disposition

In addition to what is described in the CTP (section 6.1), date of first subject visit, date of last subject visit, and duration of trial period for each site and for all enrolled subjects will be provided. Also the number of subjects enrolled, the number of subjects randomised, and the number of subjects randomised to each treatment group will be presented by site.

The reason for leaving the trial will be presented as described in the CTP (section 11.3.1).

## 6.4 Demographics and other Baseline Considerations

The demographics and other baseline (screening visit) characteristics will be presented as described in the CTP (section 11.3.2).

Concurrent diagnoses (except Psoriasis Vulgaris) including indications for concomitant medication at screening for concurrent medications and concurrent procedures at screening visit. Concurrent diagnosis coded with the MedDRA preferred term of "psoriasis" will be excluded from the summary tables.

Concurrent medications started before screening visit will be presented, which are defined as those started before screening visit or marked as "before".

Similarly, concurrent medications started after screening visit will be presented in a separate table, which are defined as those started after screening visit or, marked as "after", or those started on or after the screening visit.

In addition to what is described in the CTP, the time interval (days) from visit 1 to each trial visit will be summarized for all randomised subjects and by treatment group.

## 6.5 Compliance

Compliance with treatment instructions will be presented as described in the CTP (section 11.3.3).

## 6.6 Analysis of Efficacy

### 6.6.1 Primary Efficacy Criteria

The primary endpoint will be analysed as described in the CTP (section 11.3.4).

In addition, the difference (LEO 90100 foam – Dovobet® ointment) in the proportion of subjects with overall improvement rate, its 95% confidence interval will also be presented. Refer to CTP (11.3.11) for the imputation method.

For subjects who completed the trial before 4 weeks of treatment due to achieving substantial resolution, use the latest available results for LOCF imputation. This approach of imputation is legitimate under the assumption of short exposure time and type of population included; a re-lapse on the disease in the target area will not be expected.

### 6.6.2 Secondary Efficacy Criteria

The secondary endpoints will be analysed as described in the CTP (section 11.3.5).

There are two different descriptions on total sign score in the CTP (Section 5.2):

- The change in the total sign score from Visit 1 to Visit 4; total sign score is defined as the sum of the scores from the 3 clinical signs assessing severity in the target lesion.

- The change in the sum of the scores (total sign score) for the severity of the three clinical signs (thickness, scaliness, redness) from Visit 1 to the sum of the scores at Visit 4 (end of Week 4) for the target lesion

Since these two endpoints are the identical endpoint, both of them will be regarded as "the change in the total sign score for the target lesion from baseline to Visit 4".

Total sign score is treated as missing when the score for at least one of the clinical signs is missing. LOCF will be used to impute any missing values for Visit 4 for the analysis of change in total sign score from baseline to Visit 4 (end of Week 4).

### 6.6.3 Exploratory Efficacy Criteria

The exploratory analysis of efficacy will be presented as described in the CTP (section 11.3.6).

In addition to what is stated in the CTP, the followings will also be analysed:

The treatment difference of the change in each clinical sign (thickness, scaliness and redness) at Visit 4 will be estimated with an ANOVA with treatment as fixed effect.

For the analysis of change in score for the severity of each clinical sign from baseline to Visit 4 (end of Week 4), LOCF will be used to impute any missing values for Visit 4.

### 6.6.4 Exploratory Efficacy Criteria of Subject Assessments

The subject assessments for "time spent for application" and "ease of application" will be presented as described in the CTP (section 11.3.7). The tabulations will be provided for the full analysis set.

The subject's assessment of "time spent for application" of trial medication will be compared between the treatment groups using ordinal logistic regression. The odds ratio (odds of being less time applying LEO 90100 foam group relative to Dovobet® ointment group), its 95% CI, and a p-value will be calculated from the logistic model.

The subject's assessment of "ease of application" of trial medication will be compared between the treatment groups using ordinal logistic regression. The odds ratio (odds of being very easy applying LEO 90100 foam group relative to Dovobet® ointment group), its 95% CI, and a p-value will be calculated from the logistic model.

This analysis will be performed using full analysis set.

## 6.7 Analysis of Safety

The analysis of safety will be based on the safety analysis set as described in the CTP (section 11.3.8).

### 6.7.1 Exposure

In addition to what is stated in the CTP (section11.3.3), the number of days of exposure will be calculated as the date of final application minus the date of first application plus 1,

ignoring any interim missing applications. The duration of exposure to treatment (weeks) will be derived as the number of days of exposure divided by 7, and will be summarized for each treatment group using the mean, SD, median, minimum and maximum values. The sum of duration of exposures to treatment will be presented as all subjects-treatment-weeks.

### 6.7.2 Adverse Events

AEs will be analysed as described in the CTP (section11.3.8.1), with the following additions and clarifications.

Three tables will be produced counting AEs by each causal relationship; not related, possibly related and probably related, respectively.

If different categories of causal relationship were observed for the same SOC and preferred term in one subject, count as one event for each causal relationship.

In addition, three causal relationships will be divided into two categories; "not related" and "related" (possibly related and probably related), and a table for "related" events will be presented. If several events are observed for the same SOC and preferred term in one subject, count as one event for the greatest causality.

Separate tables for "lesional/perilesional" and "distant" cutaneous AEs will also be produced.

Adverse drug reactions are defined as adverse event that is related to trial medication:
Adverse event that is related to trial medication are those classified as the probable or possible relationship to trial medication.

### 6.7.3 Laboratory Data

The analysis of laboratory parameters will be performed as outlined in the CTP (section 11.3.8.2).

In principle, the value measured at Visit 1 is used as baseline. If the value is missing at Visit 1 but there is a measurement prior to first application of trial medication, then this measurement will be considered as the baseline value for laboratory safety examinations.

## 6.8 General Principles

### 6.8.1 Handling of Drop-outs and Missing Values

A LOCF approach will be used to impute missing values at Visit 4 (end of week 4) for the primary endpoint as described in the CTP (section 11.3.11).

LOCF will be used to impute missing values for the analysis of change from baseline to Visit 4 (end of week 4) in the sum of total sign score and the analysis of change from baseline to Visit 4 (end of week 4) in change in score for the severity of each clinical sign.

### 6.8.2 Windowing

The “by visit tabulations” will include all subjects that attended the specific visit, irrespective of whether the date of the visit was within or outside the scheduled visit window.

### 6.8.3 Other

Subjects in the trial have to be Japanese, and this requirement was an inclusion criterion. The EDC system requires a field to be completed for race, with the standard categories of white, black, Asian, or other. Therefore since the sites confirmed all subjects to be Japanese, the appropriate category for Japanese is Asian. Hence in the eCRF the “Race” field was auto populated as "Asian". However, data for this categorisation of race (Asian) does not appear anywhere in the CSR in text, listings or tables; it will only be described in the text of the CSR that all subjects were Japanese, as confirmed by the fulfilment of the inclusion criteria.

“Single quote” is used instead of “apostrophe” mark in CO (Comments) domain in statistical analysis.

### 6.8.4 Definition of Unit and Rounding Digit

Definition of unit and rounding digit is shown below:

Table [1]: Demographics:

| Category | Unit | Rounding Digit |
|---|---|---|
| Height | [cm] | 0.1 |
| Weight | [kg] | 0.1 |
| Age | [years] | 1 |
| BMI | [kg/m^2] | 0.1 |
| Duration of psoriasis | [days] | 1 |
| Duration of exposure to treatment | [weeks] | 0.1 |
| Time interval | [days] | 0.1 |
| Scores for efficacy | - | 0.1 |

Table [2]: Laboratory safety examinations:

| Category | Examination Component | Abbreviation | Unit | Rounding Digit |
|---|---|---|---|---|
| Haematology | Haematocrit | HCT | [%] | 1 |
| | Haemoglobin | HGB | [g/dL] | 0.1 |
| | Platelets | PLAT | [10^9/L] | 0.1 |
| | Erythrocytes | RBC | [10^12/L] | 1 |
| | Leukocytes | WBC | [10^9/L] | 1 |
| | HbA1c | HBA1C | [%] | 0.1 |
| Chemistry | Albumin | ALB | [g/dL] | 0.1 |
| | Alkaline Phosphatase | ALP | [U/L] | 1 |
| | Alanine Aminotransferase | ALT | [U/L] | 1 |
| | Aspartate Aminotransferase | AST | [U/L] | 1 |
| | Bilirubin | BILI | [mg/dL] | 0.1 |
| | Blood Urea Nitrogen | BUN | [mg/dL] | 1 |
| | Calcium | CA | [mg/dL] | 0.1 |
| | Calcium Corrected | CACR | [mg/dL] | 0.1 |
| | Creatinine | CREAT | [mg/dL] | 0.01 |
| | Gamma Glutamyl Transferase | GGT | [U/L] | 1 |
| | Lactate Dehydrogenase | LDH | [U/L] | 1 |
| | Phosphate | PHOS | [mg/dL] | 1 |
| | Total Protein | PROT | [g/dL] | 0.1 |
| Urine Tests | Urine Glucose | GLUC | | - |
| | Urine Protein | PROT | | - |

Statistics:

P-values are presented to a maximum of two significant figures and three decimal places. Values of p-lower than 0.001 will be specified as p<0.001.

### 6.8.5 Treatment Labels

Table [3]: Treatment labels for the clinical trial report text and tables

| Label Used in Text | Label Used in Tables | Order in Table |
|---|---|---|
| LEO 90100 aerosol foam | LEO 90100 foam | 1 |
| Dovobet® ointment | Dovobet® ointment | 2 |

# Appendix I

Tables, Figures and Listings

**Tables, Baseline Characteristics and Investigational Product Data (Module 2)**

**Tables**

101 Trial period by Site (date of first subject visit vs. date of last subject visit: Enrolled subjects

102 Subject enrolment and randomisation: Enrolled and randomised subjects

103_A Age by Site: Randomised subjects

103_B Age, height, weight, and BMI at screening visit: Randomised subjects

104 Sex by Site: Randomised subjects

105 Baseline total sign score of target lesion by Site: Randomised subjects

106 Location of target lesion and duration of psoriasis: Randomised subjects

107 Reasons for withdrawal: Randomised subjects

108 Reasons for withdrawal by last visit attended: Randomised subjects

109 Concurrent diagnoses (excluding psoriasis vulgaris) including indications of concomitant medication at screening visit by MedDRA primary SOC: Enrolled subjects

110 Concurrent medications started before screening visit by ATC: Enrolled subjects

111 Concurrent medications started after screening visit by ATC: Enrolled subjects

112 Time (days) from visit 1 to each trial visit: Randomised subjects

113 Compliance with treatment instructions: Randomised subjects

**Tables, Efficacy Data (Module 3)**

**Tables**

E1 Subjects with "overall improvement" for the target lesion at Visit 4 (Week 4 – LOCF): FAS

E1_A Subjects with "overall improvement" for the target lesion at Visit 4 (Week 4 – LOCF) by Site: FAS

E2 Subjects with "overall improvement" for the target lesion at Visit 4 (Week 4 – LOCF): PPAS

EI1 First sensitivity analysis of subjects with "overall improvement" for the target lesion at Visit 4 (Weeks 4): FAS

EI2 Second sensitivity analysis of subjects with "overall improvement" for the target lesion at Visit 4 (Week 4): FAS

EI3 Third sensitivity analysis of subjects with "overall improvement" for the target lesion at Visit 4 (Week 4): FAS

EI4 Fourth sensitivity analysis of subjects with "overall improvement" for the target lesion at Visit 4 (Week 4): FAS

E3 Subjects with "overall improvement" for the target lesion at Visit 2 and 3 (End of Weeks 1 and 2): FAS

E4 Subjects with "overall improvement" for the target lesion at Visit 2 and 3(End of Weeks 1 and 2): PPAS

E5 The change in the total sign score for the target lesion from baseline to Visit 4 (Week 4 – LOCF): FAS

E6 The change in the total sign score for the target lesion from baseline to Visit 4 (Week 4 – LOCF): PPAS

E9 The change in severity of clinical sign (redness) for the target lesion from baseline to Visit 4 (week 4 – LOCF): FAS

E10 The change in severity of clinical sign (thickness) for the target lesion from baseline to Visit 4 (week 4 – LOCF): FAS

E11 The change in severity of clinical sign (scaliness) for the target lesion from baseline to Visit 4 (week 4 – LOCF): FAS

E12 Subjects with "substantial resolution" of clinical signs for the target lesion by visit: FAS

E13 The general change for the target lesion from baseline to each visit: FAS

E14 Total sign score for the target lesion from baseline to each visit: FAS

E15 Severity of clinical sign (redness) for the target lesion from baseline to each visit: FAS

E16 Severity of clinical sign (thickness) for the target lesion from baseline to each visit: FAS

E17 Severity of clinical sign (scaliness) for the target lesion from baseline to each visit: FAS

E14_A Total sign score for the target lesion from baseline to each visit: PPAS

E15_A Severity of clinical sign (redness) for the target lesion from baseline to each visit: PPAS

E16_A Severity of clinical sign (thickness) for the target lesion from baseline to each visit: PPAS

E17_A Severity of clinical sign (scaliness) for the target lesion from baseline to each visit: PPAS

E18 Subject assessment of use of medication for "time spent for application" relative to previous topical treatment on target lesion at Visit 4 (Week 4): FAS

E19 Subject assessment of use of medication for "ease of application" relative to previous topical treatment on target lesion at Visit 4 (Week 4): FAS

E20 Summary of statistical analyses for the change in clinical signs (total sign, redness, thickness, scaliness): FAS

**Tables, Safety Data (Module 4)**

**Tables**

201 Duration and extent of exposure to treatment: Safety Analysis Set

202 Overall summary of AEs: Safety Analysis Set

203 AEs by primary SOC: Safety Analysis Set

204 AEs by primary SOC and preferred term: Safety Analysis Set

205 AEs assessed as mild by primary SOC and preferred term: Safety Analysis Set

206 AEs assessed as moderate by primary SOC and preferred term: Safety Analysis Set

207 AEs assessed as severe by primary SOC and preferred term: Safety Analysis Set

208 AEs assessed as not related by primary SOC and preferred term: Safety Analysis Set

209 AEs assessed as possibly related by primary SOC and preferred term: Safety Analysis Set

210 AEs assessed as probably related by primary SOC and preferred term: Safety Analysis Set

211 Related AEs by primary SOC and preferred term: Safety Analysis Set

212 Lesional/perilesional AEs by primary SOC and preferred term: Safety Analysis Set

213 Distant AEs by primary SOC and preferred term: Safety Analysis Set

214AEs leading to withdrawal by primary SOC and preferred term: Safety Analysis Set

215 Haematology laboratory parameters from baseline (Visit 1) to Visit 4 (Week 4): Safety Analysis Set

216 Chemistry laboratory parameters from baseline to Visit 4 (Week 4): Safety Analysis Set

217Haematology laboratory parameters categorised as low, normal or high at Visit 4 (Week 4) shown against baseline category: Safety Analysis Set

218 Chemistry laboratory parameters categorised as low, normal or high at Visit 4 (Week 4) shown against baseline category: Safety Analysis Set

219 Urinary parameters categorised as absent or present at Visit 4 (Week 4) shown against baseline category: Safety Analysis Set

**Patient Data Listings (Appendix 1)**

Listing 1.7.1 Randomisation code and treatment: Randomised subjects

**Patient Data Listings (Appendix 2)**

Appendix 2.1: Discontinued Subjects

Listing 2.1.1 Screening failures: Non-randomised subjects

Listing 2.1.2 Reason for withdrawal from trial: Randomised subjects

Appendix 2.2: Protocol Deviations

Listing 2.2.1 Major Protocol deviations: Enrolled subjects

Listing 2.2.2 Comments from CRF: Enrolled subjects

Appendix 2.3: Trial Analysis Sets

Listing 2.2.3 Inclusion/exclusion criteria met: Enrolled subjects

Listing 2.3.1 Trial analysis sets: Randomised subjects

Appendix 2.4: Demographic Data

Listing 2.4.1 Demographics: Enrolled subjects

Listing 2.4.2 Baseline characteristics: Enrolled subjects

Listing 2.4.3 Actual trial period: Enrolled subjects

Listing 2.4.4 Concurrent diagnoses (excluding psoriasis vulgaris) including indications for concomitant medication at screening visit: Enrolled subjects

Listing 2.4.5 Concurrent medications started before screening visit: Enrolled subjects

Listing 2.4.6 Concurrent medications started after screening visit: Enrolled subjects

Listing 2.4.7 Concurrent procedure: Enrolled subjects

Appendix 2.5: Compliance and/or Investigational Product Concentration Data

Listing 2.5.1 Compliance: Randomised subjects

Listing 2.5.2 Drug accountability: Randomised subjects

Listing 2.5.3 End of trial form: Enrolled subjects

Appendix 2.6: Efficacy Data

Listing 2.6.1 Severity of clinical signs for the target lesion: Enrolled subjects

Listing 2.6.2 Overall improvement for the target lesion: Enrolled subjects

Listing 2.6.3 General change in target lesion from visit 1: Enrolled subjects

Listing 2.6.4 Subject's assessment of use of medication on target lesion: Enrolled subjects

Appendix 2.7: Safety Data

Listing 2.7.1 Adverse events: Enrolled subjects

Listing 2.7.2 Severe adverse events: Enrolled subjects

Listing 2.7.3 Adverse events leading to death: Enrolled subjects

Listing 2.7.4 Serious adverse events: Enrolled subjects

Listing 2.7.5 Physical examination: Enrolled subjects

Appendix 2.8: Listing of Laboratory Values by Subject

Listing 2.8.1 Laboratory measurements: Enrolled subjects

Listing 2.8.2 Pregnancy test: Enrolled subjects

Listing 2.8.3 Abnormal laboratory measurements: Enrolled subjects

Listing 2.8.4 "Not done" reason for Laboratory test: Enrolled subjects

**Additional Tables for Results Reporting in Clinical Trial Data Registries**

Listing 2.9.1 All randomised patients: Randomised subjects

Listing 2.9.2 Subjects with adverse drug reactions: Enrolled subjects

Listing 2.9.3 Subject with serious adverse events: Enrolled subjects

Listing 2.9.4 Subjects with adverse events leading to withdrawal: Enrolled subjects

Signature Page for TMF-000126355 v1.0

| | |
|---|---|
| Reason for signing: Approved | Approv<br>Name: PPD<br>Capaci<br>Date of signature: 25-Jun-2019 09:43:42 GMT+0000 |

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