Cover Page

Study title: A Phase 3, Randomised, Investigator-blind, Active-controlled, Parallel Group, Multicentre Trial Comparing the Efficacy and Safety of 4-weeks Treatment With LEO 90100 and Daivobet® Ointment in Adult Chinese Subjects With Stable Plaque Psoriasis
LEO Pharma number: LP0053-2277
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LEO Pharma A/S

LP0053-2277

A phase 3, randomised, investigator-blind, active controlled, parallel group, multicentre trial comparing the efficacy and safety of 4 weeks treatment with LEO 90100 and Daivobet® ointment in adult Chinese subjects with stable plaque psoriasis

Statistical Analysis Plan

Version: 2.0

Parexel Project Number: 274109

Sponsor Signature Page

This document has been approved and signed electronically on the final page by the following:

Approved by: _____ _____

PPD Date

PPD ,

Biostatistical Lead

LEO Pharma A/S

Parexel Signature Page

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	PPD Project Role: Biostatistics Lead

Table of Contents

Version History

SAP Version	Date	Change	Rationale
1.0	01Dec2023	Not applicable	Original version
1.1	20Dec2023	Minor	Remove coding of light therapy (section 6.2.3). Specify 2 additional decimal places to present SD (section 4.1.1).
1.2	02Feb2024	Major	Add description of estimand strategy when there are few subjects with an IMP discontinuation due to pandemic restriction (section 4.1.5). Specify both baseline PGA strata and baseline value of the endpoint as covariate in logistic and ANCOVA model (section 4.1.5). Update SAS sample code (section 6.3.3).
1.3	29Feb2024	Minor	Update wording of estimand strategy (section 4.1.5) and add the updates to section 4.8. Change summary of lab results out of reference range from “events reported up to week 6” to “events reported up to end of study” (section 4.5.3.1) and add the updates to section 4.8.
1.4	13Mar2024	Minor	Update wording of estimand strategy (section 4.1.5). Record the change of adding baseline score value to logistic regression in section 4.8.
2.0	29Mar2024	Minor	Wording updates.

1. Introduction

This trial is conducted to assess efficacy and safety of LEO 90100 when used on the body for the treatment of stable plaque psoriasis in adult Chinese subjects, compared to Daivobet® ointment, which is approved in China for the treatment of stable plaque psoriasis on the body.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analysing study data and outlines the statistical programming specifications for the Tables, Figures and Listings (TFLs). It describes the variables and populations, anticipated data transformations and derivations and other details of the analyses not provided in the Clinical Study Protocol (CSP). In case of discrepancies between CSP and SAP (Section 4.8), the SAP supersedes the CSP.

The SAP will be finalized prior to Database Lock (DBL). The analyses described in this SAP are based upon the following study documents:

- Clinical Study Protocol, Version 3.0 (November 9th, 2022)
- electronic Case Report Form (eCRF), Version 3.0 (November 2nd, 2023)

1.1. Objectives, Endpoints, and Estimands

1.1.1. Primary objective, related endpoints and primary estimands

Table 1-1 Primary Objective, Related Endpoints and Primary Estimands

Primary Objective	Endpoints	Primary Estimands
To evaluate the efficacy of LEO 90100 compared with Daivobet® ointment on severity and extent of stable plaque psoriasis.	*Primary endpoint* • Having PGA score of 0 (clear) or 1 (almost clear) at Day 29, with at least a 2-point reduction from baseline.	• Composite strategy will be used to address permanent discontinuation of IMP not due to pandemic restrictions.[1] • Hypothetical strategy will be used to address permanent discontinuation of IMP due to pandemic restrictions.[2]
	Key secondary endpoint • Having a decrease in mPASI of at least 75% (mPASI-75) from baseline to Day 29. *Secondary endpoint* • Having a decrease in mPASI of at least 90% (mPASI-90) from baseline to Day 29.	
	CCI	• CCI

Abbreviations: AE=adverse events; CCI; COVID-19=coronavirus disease 2019; IMP=investigational medicinal product; mPASI=modified Psoriasis Area and Severity Index; mPASI-75=a decrease in mPASI of at least 75%; mPASI-90=a decrease in mPASI of at least 90%; PGA=Physician's Global Assessment of disease severity.

[1] **Permanent discontinuation of IMP not due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator's or sponsor's discretion. The timing of the event will be the date following the date of last IMP administration. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to pandemic restrictions.

[2] **Permanent discontinuation of IMP due to pandemic restrictions**: This event occurs when a subject permanently discontinues IMP for reasons related to pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines (i.e., subjects who have or have a suspicion they have COVID-19 and are not allowed on to site for visits due to quarantine measures imposed), travel limitations, subject being unable or unwilling

to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff and interruptions to the supply chain of IMP. The timing of the event will be the date following the date of last IMP administration. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to pandemic restrictions, unless caused by quarantine measures.

1.1.2. Secondary and CCI objectives and endpoints

Table 1-2 Secondary and CCI Objectives and Endpoints

Objectives	Endpoints
Secondary	
To evaluate the safety of LEO 90100 compared with Daivobet® ointment treating stable plaque psoriasis.	*Secondary endpoint* • Number of TEAEs from baseline to Day 43 per subject.
CCI CCI CCI	CCI CCI CCI CCI CCI CCI CCI

Abbreviations: CCI; CCI CCI; TEAEs=treatment-emergent adverse events.

1.2. Study Design

This phase 3, randomised, prospective, investigator-blinded, active-controlled, parallel group, multicentre trial will evaluate the efficacy and safety of 4 weeks treatment with LEO 90100 compared with Daivobet® ointment in native Chinese subjects (aged ≥ 18 years) with at least mild stable plaque psoriasis.

600 trial subjects are planned to be randomised in a 1:1 ratio to either LEO 90100 or Daivobet® ointment treatment. Randomisation will be stratified by Physician's Global Assessment of disease severity (PGA) at baseline (mild [PGA=2], moderate [PGA=3] or severe [PGA=4]).

For each subject, the trial will last 6 weeks to 10 weeks, including:

- A washout/screening period up to 4 weeks (at least 1 visit);

- A treatment period up to 4 weeks (3 visits);
- A safety follow-up period of 2 weeks (1 visit for all subjects 2 weeks after the last IMP administration).

The subjects will provide written consent according to national laws and regulations before any trial-related activities are carried out.

Washout/Screening Period

For subjects who have been receiving prohibited medications prior to screening, the screening period may be extended up to 4 weeks to ensure they complete the required washout period before they start receiving the IMP. On completion of the washout period, confirmation of the subject's ongoing eligibility for the trial will be made at Day 1 (baseline). However, if no washout is needed the subject will enter Day 1 (baseline) directly.

Treatment Period

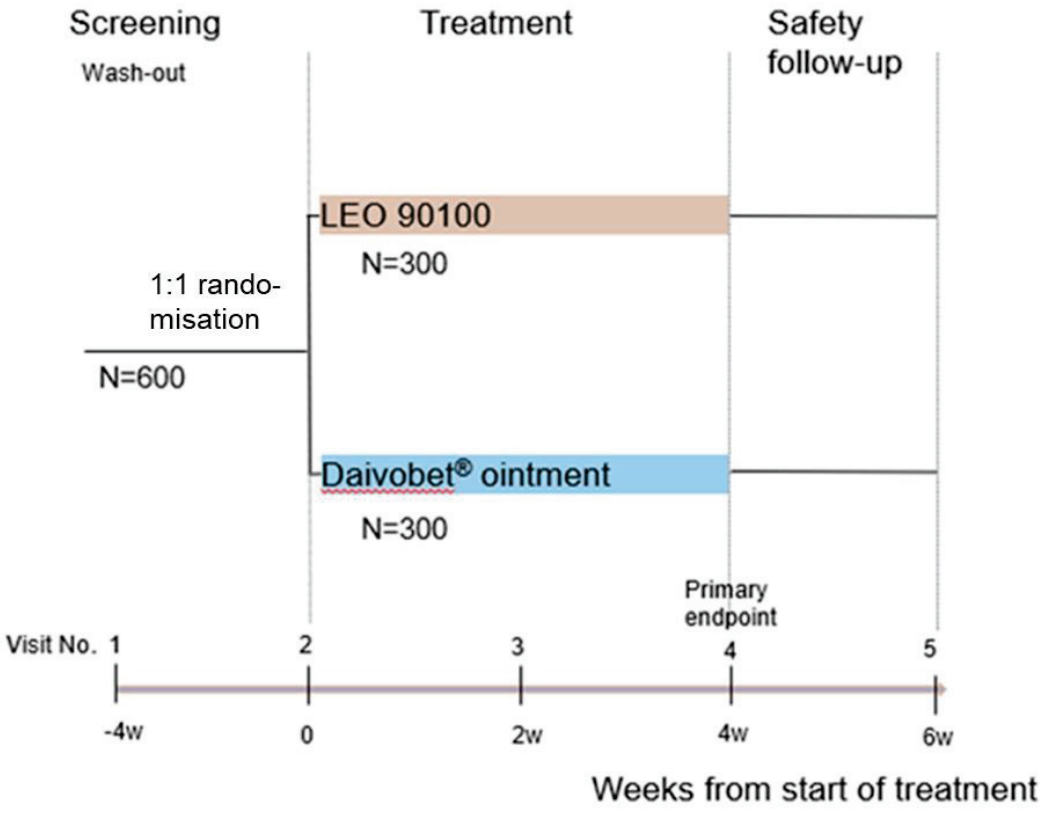
The treatment period will last for up to 4 weeks and includes 3 visits: Visit 2 (Day 1), Visit 3 (Week 2) and Visit 4 (Week 4). The start of IMP treatment will be at Day 1 and this visit will be considered as baseline. The first application of the IMP will be made at site under supervision and instruction of an unblinded member of the trial staff (not the investigator, as this is an investigator-blinded trial) at the Day 1 visit. The subjects also have the option to apply the first IMP at home after the instruction has been given at the site.

Follow-up Period

The follow-up visit (Visit 5) will be performed at Week 6, which is 2 weeks after the last visit in the treatment period.

The trial design is illustrated in Figure 1-1 and visit schedule is provided in Appendix 4.

Figure 1-1 Trial Design



Abbreviations: N=number of subjects; No.=number; w=weeks.

2. Statistical Hypotheses

The primary endpoint will first be evaluated for non-inferiority (at threshold T=CCI) and subsequently superiority 2-sided hypotheses will be tested for LEO90100 versus Daivobet® ointment.

The key secondary and one secondary endpoints will be evaluated for superiority 2-sided for LEO 90100 versus Daivobet® ointment.

Treatment effect will be defined as odds ratio (OR), and binary endpoints will be tested as follows for:

- Non-inferiority: H_0:OR $\leq$ T against H_a:OR $>$ T.
- Superiority: H_0:OR ≤ 1 against H_a:OR > 1.

2.1. Multiplicity Adjustment

The primary endpoint, the key secondary endpoint and the other secondary endpoint are included in a closing testing procedure with hierarchical tests will be used to control the overall type I error at nominal 2-sided 5% level. The hypothesis relating to a specific endpoint cannot be rejected unless all hypotheses earlier in the hierarchy are also rejected.

The confirmatory conclusions from the confirmatory testing strategy will be based on the results from the primary analyses of the primary estimands. The primary endpoint will first be evaluated for non-inferiority and if the 95% confidence interval (CI) for the treatment effect (on the OR scale) not only lies entirely above the non-inferiority threshold (T=CCI) but also above 1 then there is evidence of superiority in terms of statistical significance at the 2-sided 5% level.

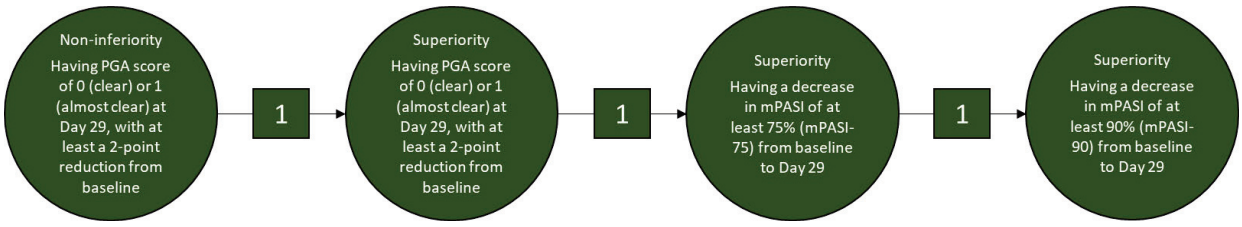
In this case, it is acceptable to calculate the p-value associated with a test of superiority and evaluate whether this is sufficiently small (two-sided p-value<0.05) to reject the hypothesis of no difference. In the switch from non-inferiority to superiority there is no multiplicity argument that affects the interpretation because, in statistical terms, it corresponds to a simple closed test procedure.

The complete superiority testing scheme is described below and illustrated in Figure 2-1. If non-inferiority is confirmed the following 3 hypotheses will be tested sequentially:

- No difference in the proportion of subjects with at least a 2-point PGA reduction from baseline having PGA score of 0 (clear) or 1 (almost clear) at Day 29 between LEO 90100 and Daivobet® ointment treatment.
- No difference in the proportion of subjects having mPASI-75 at Day 29 between LEO 90100 and Daivobet® ointment treatment.
- No difference in the proportion of subjects having mPASI-90 at Day 29 between LEO 90100 and Daivobet® ointment treatment.

The trial is considered a success if non-inferiority is confirmed for the primary endpoint. The non-inferiority margin of 10% on the OR scale, is equivalent to a non-inferiority threshold of T=CCI.

Figure 2–1 Graphical Display of Closed Testing Procedure for Primary, Key Secondary and Secondary Endpoints



Abbreviations: mPASI=modified Psoriasis Area and Severity Index; PGA=Physician's Global Assessment.

3. Analysis Sets

For purposes of analyses, the following analysis sets are defined:

Table 3–1 Subject Analysis Sets

Subject Analysis Set	Description
All screened set	All screened subjects.
All randomised subjects	All randomised subjects.
Full analysis set (FAS)	All randomised subjects. Subjects will be included in the analyses according to randomised treatment allocation. Exclusions from the FAS can be considered in special cases, as described in Section 5.2.1 (Full Analysis Set) of ICH E9 guidelines[1]. If a subject is excluded from the FAS, a justification per ICH E9 guidelines[1] will be given.
Safety analysis set	All subjects who are exposed to the IMP. Subjects will be analysed according to the treatment they actually received.

Abbreviations: FAS=full analysis set; IMP=investigational medicinal product.

The all screened set will be used for summary of subject disposition.

The all randomised subjects will be used for summary of demographic and baseline characteristics.

The full analysis set (FAS) will be used for the analysis of efficacy data and the safety analysis set will be used for the analysis of safety data.

The decisions regarding inclusion/exclusion of subjects or subject data from the analysis sets will be taken by during a blinded data review meeting and will be documented with reasons for exclusions, before unblinding of the trial.

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

4. Statistical Analyses

4.1. General Considerations

4.1.1. Statistics Presentation

Statistical analysis and generation of tables, figures, study subjects data listings, and statistical output will be performed using SAS software (SAS Institute, Cary NC), version 9.3 or later.

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

Descriptive statistics will be displayed to provide an overview of the study results. For continuous variables, descriptive statistics will include number of study subjects with available measurements (n), mean, standard deviation (SD), median, upper quartile (Q1), lower quartile (Q3), minimum, and maximum.

For categorical variables, the number and percentage of study subjects in each category will be presented. Unless otherwise noted, the denominator for percentages will be based on the number of study subjects included in the respective analysis set.

Percentages will be presented to 1 decimal place. If the percentage is 100%, a decimal will not be presented. If the count is 0, the percentage will not be presented. Typically, the % sign will be presented in the column header, but not with each individual value.

For the purpose of the tabulations, the lower and upper confidence limits for the percentages will be truncated at 0 and 100% respectively.

Decimal places for descriptive statistics will be subject to the following rules:

- “n” will be an integer.
- Mean, Q1, median and Q3 will use 1 additional decimal place compared to the original data.
- SD will use 2 additional decimal places compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

Derived variables in general will display the mean, SD, median, Q1 and Q3 to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics.

Significance tests will be 2-sided using the 5% significance level. All CIs will be presented with 95% degree of confidence, unless otherwise specified.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999".

4.1.2. Baseline Definition

Baseline measurements will be defined as the latest available observation at or prior to the date of randomisation.

Scheduled assessments taken on the same day as randomisation will be assumed as prior to randomisation. If the unscheduled assessment is recorded on the same day as randomisation, the unscheduled assessment will be assumed to be post-randomisation, unless there is clear evidence showing that the assessment is prior to randomisation.

4.1.3. Study Day

Study Day will be calculated from the randomisation date or the first IMP administration date, whichever occurs first. Study day of the randomisation or the first IMP administration date will be Day 1.

- If the date of interest is on or after the randomisation date, then:

  Study Day = [date of assessment/interest – minimum (randomisation date, first IMP administration date)] + 1

- If the date of interest is prior to the randomisation date, then:

  Study Day = [date of assessment/interest – minimum (randomisation date, first IMP administration date)]

When the date of assessment/interest is partial or missing, study day will not be calculated, unless otherwise specified.

4.1.4. Randomisation Strata

The randomisation will be stratified by PGA at baseline:

- Mild (PGA=2)
- Moderate (PGA=3)
- Severe (PGA=4)

In statistical analyses where strata are included, the stratification factors will be included as collected in the Interactive Web Response System (IWRS) at randomisation. If a subject is stratified incorrectly, "actual stratum" will be used rather than "randomised stratum".

4.1.5. Estimand Strategy

4.1.5.1. General Considerations

The analysis of endpoints related to efficacy will be based on the FAS.

An intercurrent event (IE) refers to a post-randomisation event that affects either the interpretation or the existence of the measurements of an endpoint. For the purposes of this trial, the following 2 IEs are defined:

- **Permanent discontinuation of IMP not due to pandemic restrictions:** This IE occurs when a subject permanently discontinues IMP for reasons not related to pandemic restrictions. This event can occur either at the subject's own initiative or at the investigator or sponsor's discretion. The timing of the event will be the date following the date of last IMP administration. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will be interpreted as permanent discontinuation of IMP not due to pandemic restrictions.

- **Permanent discontinuation of IMP due to pandemic restrictions:** This IE occurs when a subject permanently discontinues IMP for reasons related to pandemic restrictions. Examples of permanent discontinuation of IMP due to pandemic restrictions are quarantines (i.e., subjects who have or have a suspicion they have COVID-19 and are not allowed on to site for visits due to quarantine measures imposed), travel limitations, subject being unable or unwilling to travel to site due to personal pandemic-related reasons, site closures, reduced availability of site staff and interruptions to the supply chain of IMP. The timing of the event will be the date following the date of last IMP administration. Permanent discontinuation of IMP due to sickness with COVID-19 (an AE) will not be interpreted as permanent discontinuation of IMP due to pandemic restrictions, unless caused by quarantine measures.

Note, there is a distinction between permanent discontinuation of IMP (an IE) and withdrawal from trial and/or lost to follow-up. Withdrawal from trial and lost to follow-up, which are not IEs, will be addressed when specifying methods and/or assumptions for handling missing data. If the withdrawal from trial is related to the pandemic restrictions, missing data will be handled as missing data related to the pandemic restrictions.

The death of a subject has not been described above as an IE since occurrences of this event is considered unlikely in the setting of this trial. Should it happen that a subject dies, then analyses will handle this using the same strategy as described below for addressing permanent discontinuation of IMP due to pandemic restrictions.

The following strategies will be implemented for handling the IEs (ICH E9 [R1] guidelines[2]):

- The ‘hypothetical’ strategy attempts to quantify the effect of treatment in the hypothetical situation where IEs do not occur.
- The ‘treatment policy’ strategy attempts to quantify the effect of the decision to treat subjects with the randomised treatment, thus ignoring the occurrence of IEs.
- The ‘composite’ strategy accounts for the occurrence of IEs, through the definition of a suitable composite endpoint, whose components include the aforementioned IEs, as well as the endpoint of interest.

Depending on the strategy selected, the occurrence of an IE may lead to the exclusion of data observed after the occurrence of the event, be ignored, be accounted for in the definition of a

composite endpoint or restrict the relevant observation window to the time prior to the occurrence of the IE.

Prior to DBL, IE of permanent discontinuation of IMP due to pandemic restriction and missing data due to pandemic restriction were not observed among all subjects. Therefore, all estimand analyses will be based on the strategy of having only IE and missing data not due to pandemic restriction.

For each efficacy endpoint associated with a trial objective, a primary estimand will be pre-specified. For the binary endpoints a secondary estimand will be used to further aid in the interpretation of the results (see Section 4.1.5.2 and Section 4.1.5.3).

The following primary and secondary estimands will be defined:

- The primary estimand for binary endpoints will use a 'composite' strategy to handle IEs for subjects who have permanently discontinued IMP independently of pandemic restrictions prior to the Week 4 visit (Visit 4). Subjects will be imputed as non-responders, reflecting an assumption that permanent discontinuation of IMP independent of pandemic restrictions indicates failure of the randomised treatment to achieve response. A 'hypothetical' strategy, in the form of a multiple imputation method (see Appendix 6.3.2.1), will be used to address permanent discontinuation of IMP due to pandemic restrictions. For subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 (Visit 4) data collected after permanent discontinuation of IMP will be replaced by model-based predictions.
- Differently from the primary estimand for the binary endpoints, the secondary estimand for binary endpoints will use "treatment policy" strategy to handle IEs for subjects who have permanently discontinued treatment independently of pandemic restrictions prior to the Week 4 visit (Visit 4). Data will be used as observed.
- The primary estimand for continuous endpoints will use the same strategies applied for the secondary estimand for binary variables.

The occurrence of IEs will be listed and summarised by treatment group. Table 4-1 presents an overview of how observed and missing data will be handled according to the IEs for the primary analysis for estimands.

Table 4–1 Handling of Observed and Missing Data According to the IEs for the Primary Analysis for Estimands

IE	Data observed or missing	Estimands for binary endpoints		Estimand for continuous endpoints
		Primary	Secondary	Primary
Permanent discontinuation of IMP **not due to pandemic** restrictions	Observed	**Composite:** N/A, value of the endpoint is determined by the IE (non-response)	**Treatment policy:** Used as observed	**Treatment policy:** Used as observed
	Missing	N/A, value of the endpoint is determined by the IE (non-response)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
Permanent discontinuation of IMP **due to pandemic** restrictions	Observed	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)	**Hypothetical:** Treated as missing, MI (MAR within treatment arms)
	Missing	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)
No IE	Observed	Used as observed	Used as observed	Used as observed
	Missing **not due to pandemic** restrictions	NRI	MI (MAR within treatment arms)	MI (MAR within treatment arms)
	Missing **due to pandemic** restrictions	MI (MAR within treatment arms)	MI (MAR within treatment arms)	MI (MAR within treatment arms)

Abbreviations: IE=intercurrent event; IMP=investigational medicinal product; MAR=missing at random; MI=multiple imputation, N/A=not applicable; NRI=non-responder imputation.

4.1.5.2. Estimand Strategy for Binary Endpoints

Evaluation of non-inferiority as well as superiority for LEO 90100 versus Daivobet® ointment will be based on the Wald-type test statistic for the estimated treatment effect from a logistic regression model, adjusted for baseline PGA.

The main analysis is based on the following assumptions:

1. Missing data will be handled according to Table 4-1.
2. Use of prohibited medication and procedures will be assumed to have no influence on the endpoint of interest among subjects not discontinuing IMP.

For each of the imputed datasets, estimates of the treatment effect along with the associated standard errors will be kept on the log-scale. The pooled estimate of risk difference and OR at Week 4, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the logistic regression of the imputed data sets and transforming to the odds-scale.

The logistic regression will include both baseline PGA and the baseline score value of the endpoint (eg, continuous mPASI, CCI category) for binary endpoints other than PGA.

Primary Analysis of the Primary Estimand

The purpose of 'hypothetical' strategy is to predict what value the estimands variable would take if the given subject would not permanently discontinue IMP due to pandemic restrictions, assuming a similar course of events as experienced by subjects from the same treatment arm who have not permanently discontinued IMP due to pandemic restrictions. With this purpose in mind 2 questions naturally arise because of the composite strategy used to address permanent discontinuation of IMP independent of pandemic restrictions:

1. Would the subject still have been on treatment at Week 4 as opposed to having permanently discontinued IMP independently of pandemic restrictions beforehand?
2. If yes, would the subject have had binary response (0/1) with a 2-point reduction from baseline at Week 4?

In practice, both of these hypothetical questions will be addressed, although in reverse order, by carrying out the following steps:

1. Under missing at random (MAR) assumption within treatment arm, binary response at Week 4 (or Week 2) will be imputed for subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 (or Week 2) and for subjects who have not permanently discontinued IMP prior to Week 4 (or Week 2) and whose score at Week 4 (or Week 2) is missing due to pandemic restrictions. Fully conditional specification (FCS) method will be implemented to impute missing binary responses by implementing logistic or regression methods (number of imputed datasets = 1000; seed = 2)[3]. FCS logistic regression will be implemented for the binary PGA and CCI endpoints. FCS linear regression will be utilised to impute the mPASI score. Binary mPASI-75 and mPASI-90 will be derived from the imputed score. Response at Week 4 (or Week 2) will be imputed using the stratification PGA, the value baseline score value (not for PGA as it coincides with the randomisation strata) and response at the Week 2 visit (not applicable when imputing data for Week 2) as covariates.
2. Non-responder imputation will be applied for subjects who have not permanently discontinued IMP prior to Week 4 (or Week 2) and whose binary response at Week 4 (or Week 2) is missing for reasons other than pandemic restrictions.
3. A logistic regression model will be implemented to estimate each subject's probability of permanent discontinuation of IMP not due to pandemic restrictions up until Week 4 (Day 29) among subjects who permanently discontinued IMP due to pandemic restrictions. Stratification PGA, sex and age will be utilised as covariates. Using the subject predicted probability (p_i) of discontinuation, the following steps will be followed to derive the treatment adherence variable:
    a. For each imputed dataset, a value from the exponential distribution with rate p_i will be drawn and multiplied with 29 to obtain days (starting seed = 3)
    b. Person-days already spent in the trial will be added to the drawn number
    c. Derive the treatment adherence variable with the following categorisation:
        - Days <15: subject discontinued before Week 2
        - 15 ≤ Days < 29: subject discontinued after Week 2 and before Week 4
        - Days ≥ 29: the subject did not discontinue.

d. For subjects predicted to be discontinued before Week 2 or Week 4, non-responder imputation will be applied to the visits after the predicted discontinuation.

Table 4–2 Hypothetical Strategy for Addressing Permanent Discontinuation of IMP Due to Pandemic Restrictions and Handling of Missing Data in the Primary Analysis of the Primary Estimand

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute binary (0/1) response at Week 4 under MAR assumptions within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4.	Hypothetical strategy
		Subjects who have not permanently discontinued IMP prior to Week 4 and whose score at Week 4 is missing due to pandemic restrictions.	Handling of missing data
2	Impute binary (0/1) response at Week 4 based on NRI	Subjects who have not permanently discontinued IMP prior to Week 4 and whose score at Week 4 is missing for reasons other than pandemic restrictions.	Handling of missing data
3	Impute treatment adherence status at Week 4 within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4.	Hypothetical strategy

Abbreviations: IMP=investigational medicinal product; MAR=missing at random; NRI=non-responder imputation.

Sensitivity Analysis of the Primary Estimand

For the sensitivity analysis, which is rather conservative against the LEO 90100 group, observed data at Week 4 will be used in the Daivobet® ointment group for the subjects who permanently discontinued IMP not due to pandemic restrictions. In addition, missing data for subjects in the Daivobet® ointment group will be imputed, as described in Point 1 of hypothetical strategy summarised in Table 4–2.

Primary Analysis of the Secondary Estimand

For the primary analysis of the secondary estimand, under MAR assumption within treatment arm, binary response at Week 4 will be imputed for subjects who have permanently discontinued IMP due to pandemic restrictions prior to Week 4 and for subjects who have not permanently

discontinued IMP prior to Week 4 and whose score at Week 4 is missing due to pandemic restrictions. FCS method will be applied, as described for the primary analysis of the primary estimand.

4.1.5.3. Estimand Strategy for Continuous Endpoints

With the treatment policy strategy, subjects who have permanently discontinued IMP independently of pandemic restrictions prior to the endpoint Visit 4 (Week 4) will be included in the analysis with the actually observed score at this Visit.

Permanent discontinuation of IMP due to pandemic restrictions will be addressed by a hypothetical strategy. Data collected after such an event will not be applied in the analysis. The hypothetical scenario envisaged is that permanent discontinuation of IMP due to pandemic restrictions would not occur, assuming subjects who have experienced this event would respond like subjects from the same treatment arm who have not experienced it. The hypothetical strategy and the handling of missing data in the primary analysis are outlined in Table 4–3.

Table 4–3 Hypothetical Strategy for Addressing Permanent Discontinuation of IMP Due to Pandemic Restrictions and Handling of Missing Data in the Primary Analysis of the Primary Estimand for Continuous Secondary Endpoints

Step no.	Description	Subjects in scope for imputation	Purpose
1	Impute score at the endpoint visit under MAR assumptions within treatment arm	Subjects who have permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit.	Hypothetical strategy
		Subjects who have not permanently discontinued IMP due to pandemic restrictions prior to the endpoint visit and whose score at the endpoint visit is missing.	Handling of missing data

Abbreviations: IMP=investigational medicinal product; MAR=missing at random.

The imputation of scores will be carried out like the imputation of mPASI scores for the primary estimand of the primary endpoint (FCS linear regression with stratification PGA, value of the continuous variable at baseline and Week 2 as covariates). Data collected from subjects who have permanently discontinued IMP independently of pandemic restrictions will be included when applying this multiple imputation method (see Appendix 6.3.2.1), in alignment with the treatment policy strategy used for addressing occurrences of that IE.

Each of the imputed data sets will be analysed based on an analysis of covariance (ANCOVA) model, including treatment arm, and adjusting for the stratification PGA and baseline score as covariates. The pooled estimate of the difference in the least-square (LS)-mean change from baseline at Week 4, along with the associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the ANCOVA analyses of the imputed data sets.

4.2. Primary Endpoint Analysis

4.2.1. Definition of Endpoint(s)

The primary endpoint is having PGA score of 0 (clear) or 1 (almost clear) at Day 29, with at least a 2-point reduction from baseline.

4.2.2. Analytical Approach

The primary endpoint will be analysed following the estimand strategy for binary endpoints described in Section 4.1.5.1 and Section 4.1.5.2, including a primary and a sensitivity analysis of the primary estimand, and a primary analysis on the secondary estimand.

The non-inferiority and superiority 2-sided hypothesis, described in Section 2, will be tested for LEO 90100 vs Daivobet® ointment based on the primary analysis for the primary estimand.

A summary of PGA by visit will be provided by treatment group and overall.

A by-subject listing for PGA data will also be provided.

4.3. Secondary Endpoint Analysis

4.3.1. Key Secondary Endpoint

4.3.1.1. Definition of Endpoint(s)

The key secondary endpoint is having a decrease in mPASI of at least 75% (mPASI-75) from baseline to Day 29.

4.3.1.2. Analytical Approach

The binary key secondary endpoint will be analysed following the estimand strategy for binary endpoints described in Section 4.1.5.1 and Section 4.1.5.2. The superiority 2-sided hypothesis, described in Section 2, will be tested for LEO 90100 vs Daivobet® ointment based on the primary analysis for the primary estimand.

4.3.2. Secondary Endpoint

The secondary endpoint is having a decrease in mPASI of at least 90% (mPASI-90) from baseline to Day 29.

The planned analysis on the secondary endpoint is the same as the key secondary endpoint (mPASI-75) as described in Section 4.3.1.

4.4. CCI

CCI include:

CCI related to primary objective:

- CCI
- CCI

CCI

- CCI
- CCI
- CCI

The binary CCI will be analysed following the primary estimand strategy for binary endpoints described in Section 4.1.5.1 and Section 4.1.5.2. The continuous CCI CCI will be analysed following the estimand strategy for the continuous endpoints, as per Section 4.1.5.3.

A summary of the change from baseline in continuous variables (mPASI, CCI) will be provided by visit, by treatment group and overall, for observed values.

Observed proportions of categorical variables [redacted] will be summarized by visit, by treatment group and overall.

By-subject listing will be provided for data on mPASI, [redacted] score.

4.5. Safety Analyses

All safety analyses will be made on the safety analysis set.

4.5.1. Extent of Exposure

The duration of exposure to IMP in a specific week interval will be calculated as the number of days from date of first IMP administration in that period to the date of last IMP administration in that period, both days included.

Exposure to IMP will be presented as days and weeks of exposure.

Patient years of exposure is the duration of exposure to IMP in years:

Patient years of exposure (years) = (date of last IMP administration – date of first IMP administration + 1)/365.25

Patient years of observation is the duration of observation in years:

Patient years of observation (years) = (date of end of study – date of first IMP administration + 1)/365.25

The total amount of IMP used (g) by each visit interval is collected in the eCRF.

The total amount of IMP used (g) during the total treatment period will be calculated as the sum up of IMP used per visit. If the amount of IMP used is missing for any performed visit, the total amount of IMP used during the total treatment period will be set to missing.

The average weekly amount of IMP used (g) will be calculated as total amount of IMP/duration of exposure × 7.

The following summaries will be presented for each treatment group:

- Exposure to IMP (days/weeks of exposure to IMP) during the total treatment period.

- Total exposure to IMP (weeks) for all subjects during the total treatment period.
- Patient years of exposure and patient years of observation.
- Total patient years of exposure and patient years of observation for all subjects.
- The average weekly and total amount of IMP used (g) by each visit interval and the total treatment period.
- Number and percent of subjects with overdose (any dose of study drug used greater than 105 g within one week).

By-subject listings will be provided for IMP administration, IMP accountability, and exposure to IMP.

4.5.2. Adverse Events

AEs will be coded during the course of the trial according to the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0 or later). AEs will be presented by primary system organ class (SOC) and preferred term (PT).

Treatment-emergent AEs will be summarised; however, all AEs recorded during the course of the trial will be included in subject data listings. An event will be considered treatment-emergent if it started after the first IMP administration or if it started before the first IMP administration and worsened in severity after the first IMP administration. The tabulations described in the following will only include the treatment-emergent AEs. In each of the tabulations, AEs are defined by MedDRA PTs within primary SOC.

Unless otherwise specified, AEs will be summarised in terms of the number of subjects with at least 1 event, the percentage of subjects with at least 1 event, the number of events and the event rate per 100 patient years of exposure, and the tables will only include treatment-emergent AEs reported in the treatment period.

Event rate = (number of events/patient years) ×100.

Related AEs are defined as AEs for which the investigator has not described the causal relationship to the IMP as ‘not related’.

An overall summary will be presented for subjects with any treatment-emergent AEs in the following categories:

- Any treatment-emergent AEs
- AEs leading to Deaths
- Serious adverse events (SAEs); Non-Serious adverse events
- AEs leading to permanent discontinuation from IMP
- AEs leading to withdrawals from the trial
- Treatment-related AEs
- Severe AEs
- Outcome of AEs
- Action taken with IMP

The overall summary table will also be provided for:

- All treatment-emergent AEs reported in treatment period and the safety follow-up period. Event rate will be per 100 patient years of observation.

  Patient years of observation (years) = (date of end of study – date of first IMP administration + 1)/365.25.

- Treatment-emergent AEs reported in safety follow-up period. Event rate will be per 100 patient years of safety follow-up.

  Patient years of safety follow-up (years) = (date of end of study – date of last IMP administration)/365.25.

- Lesional/Perilesional Treatment-emeregent AEs reported in treatment period. Event rate will be per 100 patient years of exposure.

- Serious Treatment-emeregent AEs reported in treatment period. Event rate will be per 100 patient years of exposure.

- Treatment-emeregent AEs leading to withdrawals from the trial reported in treatment period. Event rate will be per 100 patient years of exposure.

Tabulations by SOC and PT will be presented for treatment-emergent AEs started in the treatment period for the following categories:

- All AEs
- Related AEs
- AEs by severity
- AEs by causal relationship to IMP
- Most frequent AEs (≥5% in any treatment group)
- Lesional/Perilesional AEs
- SAEs
- AEs leading to withdrawal from trial
- AEs leading to permanent discontinuation of IMP

Tabulations by SOC and PT will also be provided for treatment-emergent AEs started in treatment period and the safety follow-up period (event rate based on 100 patient years of observation) and treatment-emergent AEs started in the safety follow-up period (event rate based on 100 patient years of safety follow-up).

In the summary of AEs by severity, if an AE worsens in severity, the severity will be reported as the most severe recording for that AE. In the summary of causal relationship to IMP, subjects will be counted only once in the most related category (e.g. probably related). If the severity or relationship is missing, the AE will be counted as “severe” or “probably related”. The number of missing severity/relationship will be stated in the footnote of summary tables, and the listing will display the actual missing severity/relationship.

The following by-subject listings will be provided:

- All AEs
- SAEs
- AEs leading to withdrawal from trial
- AEs leading to permanent discontinuation of IMP
- AEs occurred after the first overdose of IMP

The detailed listing will provide an overview of the individual cases and include the age and sex of the subject, treatment received at the time of AE onset, the AE preferred and reported terms,

causality and severity of the AE, the action taken with the IMP, AE outcome, start and stop date of AE, duration of AE and number of days since first and last IMP administration. No narratives will be given except for SAEs and pregnancies.

Other events involving IMP (medication error, misuse and abuse of IMP) will be tabulated by treatment. Event rate will be calculated based on 100 patient years of exposure. Other events involving IMP will also be listed. No narratives will be given.

4.5.3. Additional Safety Assessments

4.5.3.1. Clinical Laboratory Evaluation

For laboratory parameters, the absolute values as well as the changes from baseline will be summarised by visit for each treatment group.

A shift table will be produced for chemistry parameters showing the categories (“Low”, “Normal”, “High” according to the normal range) at baseline against those at each post-baseline visit.

For subjects with post-baseline values, out of reference range events reported up to end of study will be summarised.

A by-subject listing will be provided for laboratory data.

4.5.3.2. Physical Examination and Other Observations Related to Safety

For physical examination, abnormalities at baseline and end-of-treatment (or early termination) as well as the transition from baseline to end-of-treatment (or early termination) will be summarised for each treatment group.

A by-subject listing will be provided for physical examination data.

Urine and Serum pregnancy test performed, reasons why not performed, and test results (“positive”, “negative”) will be listed.

4.6. Other Analyses

4.6.1. Other Variables and/or Parameters

4.6.1.1. Health Economics

Health economics parameters are not evaluated in this trial.

4.6.1.2. CCI [redacted]

The analysis on CCI [redacted] are described in Section 4.4.

4.6.2. Subgroup Analyses

Subgroup analysis is not planned in this trial.

4.6.3. Pharmacokinetics, Pharmacokinetic-Pharmacodynamic Relationships

Pharmacokinetic or pharmacodynamic parameters are not evaluated in this trial.

4.7. Interim Analysis

No interim analysis is planned during the trial.

4.8. Changes to Protocol-planned Analyses

Baseline PGA is added as a covariate to the ANCOVA model for continuous endpoints, which is not mentioned as a covariate in Protocol section 9.3.5.3.

The MedDRA search term in Protocol section 9.3.9.1 will not be applied to AE summary.

For subjects with post-baseline values, out of reference range events reported up to end of study will be summarised, instead of up to week 6 in Protocol section 9.3.9.3.

5. Sample Size Determination

Data from the EU SmPC is used for the sample size calculation[4]. Table 5–1 shows results from a historical comparative trial on the "Percentage of subjects with 'treatment success' according to the PGA of the body at Week 4 (PGA 0/1)". These data from the SmPC give a relative risk of 1.27 and a crude OR of 1.59 in favour of LEO 90100.

Table 5–1 EU SmPC Trial Result

Data from SmPC	LEO 90100	Daivobet® ointment
Trial Three	(N=141) 54.6%	(N=135) 43.0%

Abbreviations: SmPC=Summary of Product Characteristics.

Table 5-2 illustrates the power with 600 subjects randomised 1:1. The probability of superiority and non-inferiority is found by running 10,000 simulations using the data from the EU SmPC. The responder probabilities are used in a binomial sampling of the number of subjects with treatment success. For each of the simulations, the OR with 95% CI limits is calculated using Fisher's exact test and the lower 95% boundary is used to evaluate superiority and non-inferiority at the thresholds 1 and CCI respectively.

Table 5-2 Simulated Power

Endpoint	Proportion responders for Daivobet® ointment	Proportion responders for LEO 90100	Probability of superiority	Probability of non-inferiority with a NI margin OR=CCI	Probability of point estimate for LEO 90100 exceeds Daivobet® ointment (OR > 1)
PGA 0/1 at Day 29	43.0%	54.6%	0.799	0.9198	0.9975

Abbreviations: NI=non-inferiority; OR=odds ratio; PGA=Physician's Global Assessment of disease severity.

6. Supporting Documentation

6.1. Appendix 1: List of Abbreviations

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
CCI	CCI
CI	Confidence interval
CSP	Clinical Study Protocol
eCRF	electronic Case Report Form
DBL	Database Lock
CCI	CCI
EDC	Electronic Data Collection
FAS	Full Analysis Set
FCS	Fully Conditional Specification
ICF	Informed consent form
ICH	International Council for Harmonisation
IE	Intercurrent Event
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
LS	least square
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
(m)PASI	(modified) Psoriasis Area and Severity Index
NRI	Non-Responder Imputation
OR	Odds Ratio
PGA	Physician's Global Assessment of disease severity
CCI	CCI
CCI	CCI
PT	Preferred Term
CCI	CCI
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
CCI	CCI
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures and Listings
WHO	World Health Organization

6.2. Appendix 2: Supporting Study Information

6.2.1. Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided based upon all screened subjects, from screening to study completion.

The number of subjects in the following categories will be summarized based on the all screened set:

- Subjects screened (i.e. signed informed consent)
- Subjects passed screening
- Subjects failed screening
    - The criteria not satisfied
- Subjects met all eligibility but discontinued before randomisation

Disposition of subjects for treatment completion and study completion will be summarized by treatment group and overall. The number and percentage of subjects in the following categories will be summarized based on all randomised subjects.

- Subjects randomised
- Subjects randomised but not treated
- Subjects treated (with at least one dose of IMP)
- Subjects included in Full Analysis Set
- Subjects included in Safety Analysis Set
- Subjects completed treatment
- Subjects permanently discontinued IMP (including reasons of IMP discontinuation)
- Subjects completed study
- Subjects discontinued from study (including reasons of study discontinuation)

A summary of the number and percentage of subjects in each analysis set (FAS, safety analysis set) will be provided. Percentage will be based on all randomised subjects.

The following by-subject listings will be provided:

- Subjects disposition with their screening and withdrawal/study completion details (including reason for discontinuation) (all screened set)
- Subjects randomisation assignment with stratification factors (all randomised subjects)
- Subjects analysis set assignment (all randomised subjects)

6.2.2. Demographics

Descriptive statistics of demographics will be presented for all randomised subjects by treatment group.

- Age (years)
- Age categories (≤ 35 years, 36-50 years, 51-64 years, ≥65 years)
- Sex (Male, Female)
- Is child-bearing potential (Yes, No)
- Race (Chinese)

A by-subject listing of demographic for all randomised subjects will be provided.

6.2.3. Baseline and Disease Characteristics

Descriptive statistics of baseline and disease characteristics will be presented for all randomised subjects by treatment group.

- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Fitzpatrick skin type
- Psoriasis history
    - Years of having psoriasis
    - Type of psoriasis
    - Location
- Previous anti-psoriatic treatment
    - Any previous anti-psoriatic therapy (Yes, No)
    - Treatment type
    - Medication
        - Systemic therapy and topical medications will be coded by World Health Organization (WHO) Drug Global Dictionary, version Sep 2022 or later. ATC Level 2, ATC Level 4 and PT will be summarised.

A summary of baseline values of efficacy variables will be presented for all randomised subjects by treatment group.

- PGA
- mPASI
- CCI
- CCI
- CCI
- CCI

A by-subject listing of baseline and disease characteristics for all randomised subjects will be provided.

6.2.4. Treatment Compliance

Treatment compliance will be calculated based on the duration and frequency of IMP administration:

Treatment compliance (%) = (Days with once IMP administered/duration of exposure to IMP) ×100,

Duration of exposure to IMP = date of last IMP administration – date of first IMP administration + 1.

Treatment compliance during the total treatment period will be presented for each treatment group for the safety analysis set.

A by-subject listing on treatment compliance will be provided.

6.2.5. Protocol Deviations

Protocol deviations will be handled in accordance with Parexel Standard Operating Procedures (SOPs).

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

Decisions to exclude subjects from the will be made before DBL in a blinded manner. A by-subject listing of major protocol deviations will be provided. A summary of the number and percentage of subjects with a major protocol deviation by type of deviation will be provided based on all screened subjects. PDs due to COVID-19 will be listed separately.

6.2.6. Medical History and Concurrent Illnesses

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later.

Medical history events will be summarized for randomised subjects by preferred term (PT) and system organ class (SOC) by treatment group and overall as:

- Past medical history if confirmed not to be ongoing at screening.
- Current medical history if confirmed to be ongoing at screening.

Past and current medical history will be listed separately.

6.2.7. Prior/Concomitant Medications and Procedures

Medication and/or procedure start and stop dates will be compared to the date of first IMP administration to be classified as below:

- Prior only: medications/procedures that start and stop prior to the date of first IMP administration.
- Both prior and concomitant: medications/procedures start before the date of first IMP administration and stop on or after the date of first IMP administration.
- Concomitant only: medications/procedures start on or after the date of first IMP administration.

Medications/procedures start after the completion/withdrawal date will be listed but will not be classified or summarized.

Medications will be coded using World Health Organization (WHO) Drug Global Dictionary, version Sep 2022 or later. The following medications will be summarized by Anatomical Therapeutic Chemical (ATC) code (levels 2 and 4) and PT for all randomised subjects. In case of missing level 4 coding the level 3 coding will be used.

- Prior medications
- Concomitant medications (including both prior and concomitant medications and concomitant medications)
- Rescue medications (concomitant medications indicated as rescue treatment)

Procedures will be coded using MedDRA Version 25.0 or later. Concomitant procedures will be summarized by SOC and PT for all randomised subjects.

By-subject listings will be provided for all medications and procedures with the flag of classifications for all randomised subjects.

6.3. Appendix 3: Data Handling Conventions

6.3.1. Analysis Visit Windows

6.3.1.1. Effectiveness

Visit windows are defined in Schedule of Assessments (SoA) (Appendix 4).

No visit window re-mapping will be performed. The analysis will be based on the nominal visit collected in EDC.

6.3.1.2. Safety

Visit windows are defined in Schedule of Assessments (SoA) (Appendix 4).

No visit window re-mapping will be performed. The analysis will be based on the nominal visit collected in EDC.

6.3.2. Missing Date Imputation

6.3.2.1. Missing/Incomplete AE Start Date

For analyses of AEs, a complete date must be established in order to correctly identify the AE as occurring during treatment or not. For purposes of imputing missing components of partially reported or missing start and stop dates for AEs, the algorithms listed below will be followed. Start and stop dates of AEs in the subject data listings will be displayed as reported (i.e., no imputed values will be displayed in data listings).

Partial or missing AE start dates will be imputed as follows:

Imputation of partial or missing start dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date of first dose.
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use the 1st of January of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.

- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.
- If the start date is completely unknown and the stop date is prior to the date of first dose of IMP, then set the start date to the 1st of January of the year of the stop date.

6.3.2.2. Missing/Incomplete Medication Date

If medication/procedure start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of IMP administration. Medications/procedures will be assumed to be concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication/procedure started prior to the IMP administration. If there is clear evidence to suggest that the medication/procedure started prior to the IMP administration, the medication/procedure will be assumed to be both prior and concomitant, unless there is clear evidence to suggest that the medication/procedure stopped prior to the IMP administration. If there is clear evidence to suggest that the medication/procedure stopped prior to the IMP administration, the medication will be assumed to be prior only.

6.3.3. Multiple Imputation and Rubin's Rule

Multiple imputation will be utilized to primary and secondary endpoints analysis as described in section 4.2 and 4.3.

FCS logistic regression will be implemented for the binary PGA and SGA endpoints. FCS linear regression will be utilized to impute the mPASI score.

A logistic regression or ANCOVA model will be implemented to analyse each imputed datasets and then combine the estimates by Rubin's rule.

The following SAS example code will be utilized to perform MI, ANCOVA or logistic regression, and Rubin's rule, in case of continuous or binary variables:

```
proc sort data=data; by subjid week; run;
proc transpose data=data out=datain prefix=W;
      var aval;
      by subjid trtp strata_pga baseline_value;
      id week;
run;

*/MI - full conditional logistic (PGA or SGA)/;
proc sort data=datain; by trtp; run;
proc mi data=datain out=mi_data nimpute=1000 seed=2;
      by trtp;
      class strata_pga w2 w4 baseline_value;
```

```
      var w2 w4 strata_pga baseline_value;
      fcs logistic (w2 = strata_pga baseline_value /details);
      fcs logistic (w4 = strata_pga baseline_value w2/ details);
run;
proc sort data=mi_data; by _imputation_ subjid; run;

*/MI - full conditional regerssion (mPASI)/;
proc mi data=datain out=mi_data nimpute=1000 seed=2 minimum=0 maximum=64.8;
      by trtp;
      class strata_pga;
      var w2 w4 strata_pga baseline_value;
      fcs reg (w2 = strata_pga baseline_value/ details);
      fcs reg (w4 = strata_pga baseline_value w2/ details);
run;
proc sort data=mi_data; by _imputation_ subjid; run;

*/Model for logistic regression/;
proc logistic data=parameter;
      class trt01p(ref=first) baspga;
      model aval(event="1")=baspga trt01p/ covb;
      by _imputation_;
      output out=pred_probs p=p;
      ods output parameterestimates=lgsparms;
run;

*/Apply Rubin's Rule/;
proc mianalyze parms(classvar=classval)=lgsparms;
      class trt01p;
      modeleffects trt01p;
      ods output parameterestimates=mi_lgsparms;
run;

*/Model for ANCOVA/;
proc glm data=data;
      class trtp strata_pga;
      by _imputation_;
      model aval = trtp strata_pga baseline_value /solution;
      ods output parameterestimates=param_est;
run;
data param_est;
      set param_est;
      if parameter = "trtp    LEO90100";
      keep _imputation_ estimate stderr;
run;

*/Apply Rubin's Rule/;
proc mianalyze data=param_est;
      modeleffects estimate;
      stderr stderr;
      ods output parameterestimates=mi_ancova;
run;
```

6.4. Appendix 4: Schedule of Assessments

Table 6-1 Schedule of Activities (SoA)

Procedure	Washout/ screening	Treatment period			Follow-up	Unscheduled visit[2]	Early termination[3]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**			
Day	**-28 to 1**	**1**	**15**	**29**	**43**			
Week	**-4 to 0**	**0**	**2**	**4**	**6**			
Visit window (days)[1]	**NA**	**0**	**±3**	**±3**	**±3**			
Trial population and eligibility								
Informed consent[4]	X							10.1.3
Subject eligibility	X	X						5.1; 5.2
Investigator assessments at screening/baseline only								
Demographics	X							8.1
Fitzpatrick skin type	X							8.1
Medical history[5]	X	X						8.1
Height and weight		X						8.1
Treatments								
Randomisation		X						6.3
Subject treatment instructions		X						6.1.1
Dispensing of IMP		X	X					6.2
Dispensing of subject diary		X						6.5
IMP administration		X	X			X		6.1.1
Diary recording by subjects[6]		X	X	X				6.5
Treatment compliance[7]			X	X		X	X	6.5
Return of IMP			X	X	X	X	X	6.2
Concomitant medication and concurrent procedures	X	X	X	X	X	X	X	6.9.1

Procedure	Washout/ screening	Treatment period			Follow-up	Unscheduled visit[2]	Early termination[3]	Protocol section
Visit	**1**	**2**	**3**	**4**	**5**			
Day	**-28 to 1**	**1**	**15**	**29**	**43**			
Week	**-4 to 0**	**0**	**2**	**4**	**6**			
Visit window (days)[1]	**NA**	**0**	**±3**	**±3**	**±3**			
Investigator assessments of efficacy								
PGA[8]	X	X	X	X			X	8.2.1.1
CCI	X	X	X	X			X	8.2.1.2
mPASI		X	X	X			X	8.2.1.3
CCI								
CCI		X	X	X			X	8.2.2.1
CCI		X	X	X			X	8.2.2.2
CCI		X	X	X			X	8.2.2.3
Assessments of safety								
Physical examination	X			X		X	X	8.3.1
Chemistry (vitamin D)	X	X		X	X	X	X	8.3.2; 10.2
Serum and urine calcium and creatinine (central laboratory)	X	X		X	X	X	X	8.3.2; 10.2
Serum cortisol		X		X			X	8.3.2; 10.2
Serum pregnancy test	X							8.3.3; 8.4.5; 10.2
Chemistry (albumin, potassium, sodium and urea)	X	X		X	X	X	X	8.3.2 10.2
Urine pregnancy test (at site)	X	X		X	X	X	X	8.3.3; 8.4.5; 10.2
AEs	X	X	X	X	X	X	X	8.4
End of treatment/trial								
End-of-treatment form[9]				X			X	7.1
End-of-trial form[9]					X		X	4.4

Abbreviations: AEs=adverse events; CCI [redacted]; eCRF=electronic case report form; ICF=informed consent form; IMP=investigational medicinal product; mPASI=modified Psoriasis Area and Severity Index; NA=not applicable; PGA=Physician's Global Assessment; CCI [redacted]

1 If the date of a trial visit does not fall in the visit window, subsequent visits should be planned to maintain the original visit schedule as outlined in the SoA above.

2 Assessments to be performed at unscheduled visits will be at the discretion of the investigator. The subject will be asked about AEs by the investigator.

3 Subjects who permanently discontinue IMP or withdraw from the trial will be asked to come for the primary endpoint visit and will be followed up (Protocol Section 7.1).

4 The ICF must be signed prior to performing any protocol-related procedures, including but not limited to screening evaluations and washout of prohibited medications. Screening evaluations can be either on the same date the ICF was signed or at a later date.

5 In case medical history is incomplete at screening visit, missing data will be retrieved at Day 1 (baseline).

6 To supplement the compliance check made at Visits 3 and 4, a subject diary should be completed daily during the treatment period.

7 Treatment compliance includes recording the number of applications missed by each subject (Protocol Section 6.5).

8 The body areas to be assessed are the trunk (including the neck) and the limbs, i.e., arms (including hands) and legs (including feet and buttocks). 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 IMP or assessed as part of the efficacy analysis.

9 An end-of-treatment form (Protocol Section 7.1) and end-of-trial form (Protocol Section 4.4) must be completed in the eCRF for all subjects assigned to treatment.

6.5. Appendix 5: Efficacy Assessments

6.5.1. PGA

The PGA is an instrument used in clinical trials to rate the severity of psoriasis. It is a 5-point scale measurement ranging from 0 (clear) to 4 (severe) based on degree of plaque thickening, scaling and erythema (Table 6–2). The PGA score will be assessed according to the SoA (Appendix 4). 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 6–2 Physician's Global Assessment of Disease Severity

Score	Disease severity	PGA morphological descriptors
0	Clear	Plaque thickening: No elevation or thickening over normal skin. Scaling: No evidence of scaling. Erythema: None (no residual red colouration but post-inflammatory hyperpigmentation may be present).
1	Almost clear	Plaque thickening: None or possible thickening but difficult to ascertain whether there is slight elevation above normal skin level. Scaling: None or residual surface dryness and scaling. Erythema: Light pink colouration.
2	Mild	Plaque thickening: Slight but definite elevation. Scaling: Fine scales partially or mostly covering lesions. Erythema: Light red colouration.
3	Moderate	Plaque thickening: Moderate elevation with rounded or sloped edges. Scaling: Most lesions are at least partially covered. Erythema: Definite red colouration.
4	Severe	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 colouration.

Abbreviations: PGA=Physician's Global Assessment of disease severity.

6.5.2. CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

6.5.3. mPASI

The mPASI score will be assessed according to the SoA (Appendix 4). The investigator will make assessments of the extent and severity of clinical signs of the subject's psoriasis. Assessment is not made for the face and hence, this PASI assessment is modified to exclude the face.

The **extent** of psoriatic involvement will be recorded for each of the areas (trunk [including the neck] and the limbs [such as arms and legs]; excluding any involvement on face, scalp, genitals and skin folds) 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 CCI affected (see Section 6.5.2). 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 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 the given body region, will be determined according to Table 6–3.

Table 6–3 Scale for Disease Severity

Score	Severity	Description
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 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

The following formula will be used to calculate the mPASI:

- 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 mPASI which can range from 0 to 64.8.

6.5.4. CCI

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