Cover Page

Study title: Efficacy and safety of brodalumab in adolescents from 12 to 17 years of age with moderate-to-severe plaque psoriasis; EMBRACE 1
LEO Pharma number: LP0160-1396
NCT number: NCT04305327
Date: 26-Jun-2023

Statistical Analysis Plan (SAP)

Protocol Title:	LP0160-1396
Protocol Version No./Date:	6.0/05-OCT-2021
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1.0 Approvals

Sponsor	
Sponsor Name:	LEO Pharma A/S
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Biostatistician / Title:	[redacted]
Signature /Date:	[redacted]

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
1.0/26-JUN-2023	Created as new

3.0 Table of Contents

Table of Tables

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under LEO Pharma A/S Protocol LP0160-1396.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Estimands
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol, and case report form (CRF). Any further changes to the protocol or CRF may necessitate updates to the SAP. The SAP will be finalised prior to database lock and unblinding of the study treatment codes.

6.1 Changes from Protocol

It was decided to terminate the trial ahead of time. At this time only 12 subject had been enrolled into the trial. 120 subjects were planned.

None of the objects and related endpoints as described in the protocol will be tested. This SAP outlines the planned reporting of data. All available data will be listed and key data sources will be tabulated.

As no endpoints will be tested no estimand strategies will be implemented from Section 14.3.6 of the Protocol.

No tables, figures or listings will be provided for intercurrent events, it is assumed that all patients have discontinued due to the termination of the study and that any rescue medications will be shown in the concomitant medication listing.

Further, demographic and baseline characteristics, exposure, adverse events laboratory data, Columbia-suicide severity rating scale data, Patient health questionnaire-A data, and vital sign data will be tabulated. Section 12.0 will contain details related to the scope of the analyses.

Due to the early termination of this study the following parameters have not been analysed by the external vendors and as such will not be included in this SAP:

- Electrocardiogram (ECG)
- Pharmacokinetic (PK)
- Anti-Drug Antibodies (ADA)

7.0 Study Objectives and Endpoints

Due to the early termination of the study none of the endpoints described in Section 6 of the Protocol will be assessed

8.0 Study Design

This is a clinical phase 3, randomised, placebo-controlled and comparator-controlled trial designed to evaluate the efficacy, safety, tolerability, and PK of brodalumab treatment in adolescents (from 12 to 17 years of age) with moderate-to-severe plaque psoriasis.

The trial design includes 4 periods:

- A screening period of up to 4 weeks (week -4/-2 to week 0).
- An induction period of 12 weeks (week 0 to week 12 - treatment phase).
- A maintenance period of 40 weeks (week 12 to week 52 - treatment phase).
- A safety follow-up period of 8 weeks (week 52 to week 60 - off-treatment phase).

Eligible trial participants will be randomised at week 0 (Day 1) to one of the following 4 treatment arms in a 2:2:1:1 ratio:

- Brodalumab (brodalumab for 52 weeks of treatment).
- Ustekinumab (ustekinumab for 52 weeks of treatment).
- Placebo followed by brodalumab (brodalumab placebo for the first 12 weeks of treatment and brodalumab for the last 40 weeks).
- Placebo followed by ustekinumab (brodalumab placebo for the first 12 weeks of treatment and ustekinumab for the last 40 weeks).

The brodalumab arm and the placebo arms will be double-blinded until Week 12 (Week 0 to Week 12). The ustekinumab treatment will be open-label throughout the treatment phase (Week 0 to Week 52). Brodalumab (brodalumab for 52 weeks of treatment).

8.1 Sample Size Considerations

The primary endpoint for this trial is the PASI 75 response status at week 12. Denoting the week 12 PASI 75 responder rates for the adolescent brodalumab dosing regimen and pooled placebo arms by π_{broda} and $\pi_{placebo}$ respectively, the following null hypothesis,

$$H_0: \pi_{broda} - \pi_{placebo} \leq 0,$$

will be tested versus the 1-sided alternative,

$$H_1: \pi_{broda} - \pi_{placebo} > 0,$$

by assessing if the lower limit of the 95% confidence interval (CI) for the difference in responder rates is >0 and by comparing the 2-sided p-value with the 5% significance level.

The PASI 75 composite endpoint is defined as achieving a PASI 75 response without prior discontinuation of investigational medicinal product (IMP) treatment or previously satisfying the requirements for rescue treatment. Under the assumption that the 12-week response rates for the PASI 75 composite endpoint in the adolescent brodalumab dosing regimen and pooled placebo arms are 80% and 15% respectively, a sample size of 40 subjects per arm, will provide >99% power to detect a significant treatment difference.

In addition to the primary endpoint, the precision of the estimate of the difference in vaccine response rates between the adolescent brodalumab dosing regimen and pooled placebo arms, was taken into consideration when arriving upon a final sample size.

For the purposes of the sample size calculation, the precision was taken to be half the width of the associated 95% CI for the estimated difference in the week 12 vaccine response rates between the adolescent brodalumab dosing regimen and pooled placebo arms Table 1 provides the 95th percentile for the precision of the estimated difference in vaccine response rates, from 100 000 simulations assuming the rate of vaccine response is equal in the 2 arms.

The 95% CIs were calculated based on

$$\left(p_{broda} - p_{placebo}\right) \pm 1.96 \times \sqrt{\left(\frac{p_{broda(1-p_{broda})}}{n_{broda}} + \frac{p_{placebo(1-p_{placebo})}}{n_{placebo}}\right)}$$

where p_{broda} and $p_{placebo}$ are the estimated week 12 vaccine response rates for the adolescent brodalumab dosing regimen and pooled placebo arms respectively, and n_{broda} and $n_{placebo}$ are the number of subjects randomised to the respective arms. Therefore, for a given set of assumptions regarding the sample size and response rates provided in Table 1, it would expect that the probability of obtaining a 95% CI for the difference in response rates less precise than the corresponding value in Table 1 to be ≤5%.

Table 1 Estimated one-sided 95% upper confidence limit for the precision of the estimated difference in vaccine response between the brodalumab dosing regimen and placebo arms assuming the probability of vaccine response is equal in the 2 arms

	Probability of vaccine response	
Sample size/arm	**70%**	**80%**
30	24.6%	22.8%
35	22.8%	20.8%
40	21.2%	19.5%

8.2 Randomisation

Subjects who comply with all the inclusion criteria and who do not violate any of the exclusion criteria will be randomised at week 0 to receive treatment with brodalumab, ustekinumab, placebo followed by brodalumab, or placebo followed by ustekinumab, stratified by baseline body weight (<70 kg and ≥70 kg). The treatment assignment occurs on the basis of a computer-generated randomisation scheme in a 2:2:1:1 ratio.

The IRT will be used to control randomisation and stratification factors, along with IMP supply chain and expiry tracking.

8.3 Blinding

The treatment allocations will not be shared until after database lock. The blinding and masking processes described in the Data Blinding and Documentation plan V1.0 will not be implemented due to the termination of the study. For more details see section 6.1.

9.0 Trial Analysis Sets

9.1 Screened Subjects

All screened subjects will be accounted for in the CSR.

9.2 Full Analysis Set

All randomised subjects will be included in the full analysis set (FAS). Subjects will by default be included in FAS if randomised and analysed according to the randomised treatment allocation.

9.3 Safety Analysis Set

Subjects in the safety analysis set (SAS) will be analysed based on the actual treatment and are defined as a subject who received at least one IMP (brodalumab, ustekinumab, or placebo) dose.

10.0 Conventions, Derivations and Definitions

10.1 Demographics, Baseline Characteristics

Age is calculated as informed consent/assent date – date of birth / 365.25 (Demographics and Informed consents forms). In case date of birth is not collected, use age as collected on the Demographics form. If date of birth and age are not collected on the Demographics form, use age as collected on the Randomisation form.

Body mass index (BMI) is calculated as weight (kg)/height (m)^2. BMI will be rounded to 1 decimal place.

10.2 Vital Signs

Converting temperature to Celsius according to the following formula (xF – 32) * 5/9, where x is Fahrenheit. Converted temperature will be rounded to 1 decimal place.

10.3 Adverse Events

10.3.1 Treatment-Emergent Adverse Events

A TEAE is defined as any AE starting after the first use of IMP, or started before the first use of IMP and worsened in severity after first dose of IMP (see section 10.5 for incomplete dates).

Missing values related to AEs will be treated as missing with the exception for causality, intensity and seriousness and outcome of an AE. The following rules apply:

- If causality is missing, the AE will be regarded as related to the IMP (impute to “Probably related”)
- If the intensity of an AE is missing, the AE will be regarded as severe
- If seriousness is missing, the AE will be regarded as serious
- If onset date is missing, the AE will be regarded as treatment emergent (it will be assumed to be the first day of dosing) unless the end date is before first day of dosing
- If onset date is before first dosing of IMP, and with missing stop date, and the AE is worsening in severity the AE will be regarded as treatment emergent

- If outcome is missing, and no date of outcome is present, the outcome is regarded as 'not recovered'

An AE which is "Possibly related" or "Probably related" is considered to be "Related" to IMP/vaccine.

10.3.2 Adverse Events of Special Interest

The following AEs of special interest (AESI) have been defined:

- suicidal ideation and behaviour (SIB)
- serious infections (i.e., infections meeting the criteria of being an SAE),
- malignancy diagnosed after randomisation (except basal cell carcinoma, squamous cell carcinoma of the skin, and cervical carcinoma in situ)
- and major adverse cardiac events (MACE) defined as stroke, myocardial infarction, or cardiovascular death

No manual search for AEs of special interest will be conducted. AEs of special interest collected on the adverse event form will be used.

10.4 Protocol Deviations

Per [redacted] processes, important protocol deviations data will be entered into Predictive Study Operations (PSO). The study team and the Sponsor will conduct ongoing reviews of the deviation data from PSO.

10.4.1 Protocol Deviation Categories

Categories are defined as protocol deviations as per the Protocol Deviation Guidance.

10.5 Incomplete Dates

Adverse Events

If the AE start day is missing, but AE start month and year are not missing, the following rules apply:

- If the year and month of the AE start is before the year and month of the exposure start, or if the AE end date is complete and before the exposure start, the AE will not be considered treatment emergent for while in trial
- If the year and month of the AE start is the same as the year and month of the exposure start, the AE will be considered treatment emergent and assigned to the relevant phases/periods unless the AE has a complete end date which is before exposure start
- If the year and month of the AE start is after the year and month of exposure start, it will be assumed that the AE started on the first day of the month and the AE will be assigned to the relevant phase (or safety follow-up period) accordingly

If the AE start month is missing, but AE start year is not missing, the following rules apply:

- If the year of the AE start is before the year of the exposure start, or if the AE end month and year is not missing and before the month of the exposure start and before or at the year of exposure start, or if the AE has a complete end date which is before the exposure start date, the AE will not be considered treatment emergent
- If the year of the AE start is the same as the year of the exposure start, the AE will be considered treatment emergent and assigned to the treatment period, unless the AE end month and year is not missing and before the month of the exposure start and before or at the year of the exposure start, or the AE has a complete end date which is before the exposure start date

- If the year of the AE start is after the year of exposure start, it will be assumed that the AE started on 01 January and the AE will be assigned to the treatment or follow-up period accordingly

Concomitant Medication:

For incomplete start dates of concomitant medication, the following rules apply:

- If a medication start day is missing, but start month and year are not missing, it will be assumed that the start day is the first day of the month. If the medication start day and month are missing, but start year is not missing, it will be assumed that the start day is 01 January. If the medication start day, month and year are missing, it will be assumed that the medication was started before study start.

For incomplete end dates of concomitant medication, the following rules apply:

- If a medication end day is missing, but end month and year are not missing, it will be assumed that the end day is the last day of the month. If the medication end day and month are missing, but end year is not missing, it will be assumed that the end day was 31 December. If the medication end day, month and year are missing, it will be assumed that the medication was ongoing at the end of the study.

Administration of IMP:

In case of incomplete time registrations of IMP dosing with dates of administration being available, the time of 12:00:00 will be used.

10.6 Definition of Prior and Concomitant Medication

Any medication, except for medication listed as IMP in the protocol will be regarded as concomitant medication if taken on day of the randomisation later. Any medications, except for medication listed as IMP in the protocol will be regarded as prior medication if taken on the day before randomisation or earlier.

10.7 Definition Baseline, Study Day 1

Day 1 is defined as the day of randomisation. The last measurement prior randomisation is defined as baseline.

10.8 Definition Exposure Start and End

Exposure start: Date and time of first dose.

Exposure end: Data and time of last dose.

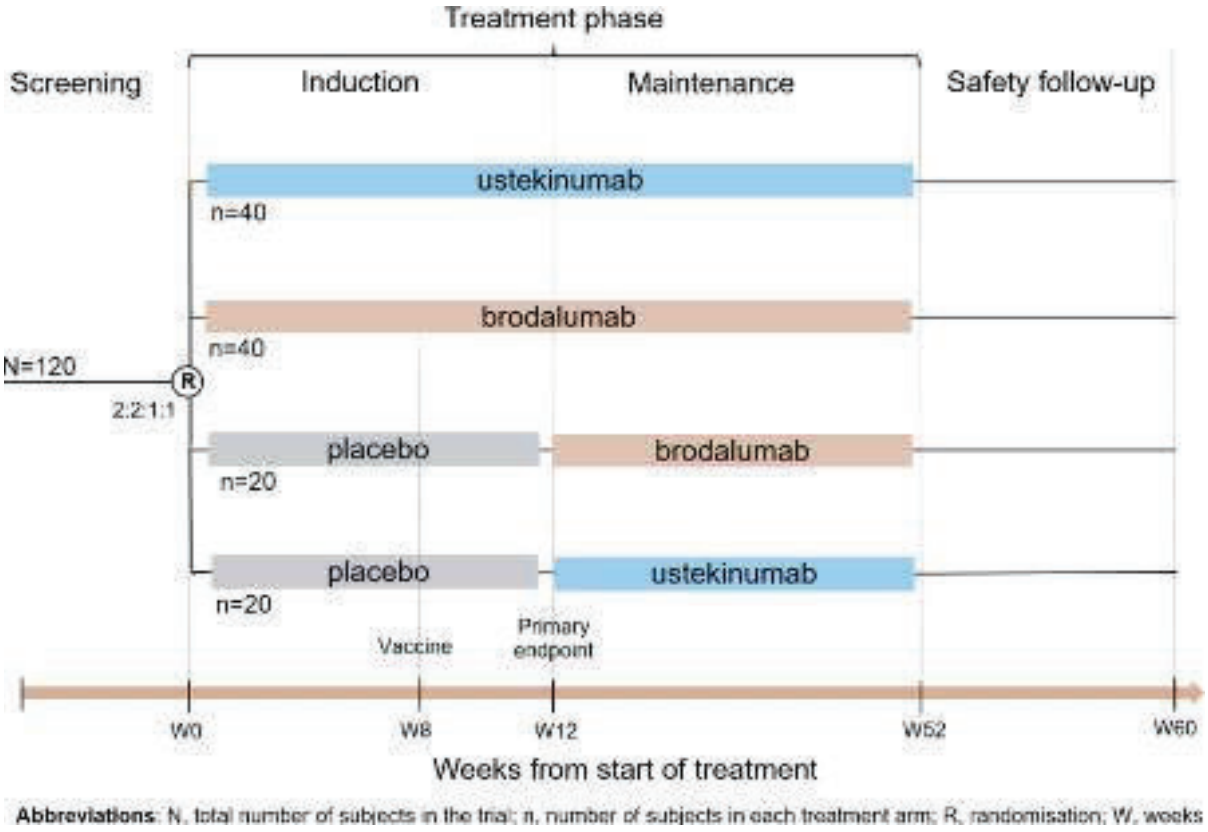
10.9 Calculation of Scores

Calculation of the scores is defined in Appendix 1 Calculation of Scores.

10.10 Treatment Arms for Analyses

Figure 1 - Treatment Arms for Analysis shows the schematic of the trial design and the four arms.

Figure 1 - Treatment Arms for Analysis



Abbreviations: N, total number of subjects in the trial; n, number of subjects in each treatment arm; R, randomisation; W, weeks

11.0 Interim Analyses

No interim analyses are planned for this trial.

12.0 Statistical Methods

12.1 General Principles

Actual treatment will be presented unless explicitly stated differently in the output. All data, as defined in the shell document, will be listed as collected without any imputations unless explicitly stated differently.

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD), median, lower and upper quartiles (Q1 and Q3), minimum, and maximum. The number of decimal places displayed for each statistic will be determined as follows:

- Mean and median: 1 more than the number of decimal places allotted in the source data.
- SD: 2 more than the number of decimal places allotted in the source data.
- Q1 and Q3: 1 more than the number of decimal places allotted in the source data.
- Minimum and maximum: equal to the number of decimal places allotted in the source data.

Whenever applicable the tabulation of data by visit will explicitly account for missing data.

For categorical data, frequency counts and percentages will be presented. Percentages will be reported to 1 decimal place.

Due to the termination of the study data will be presented by the four treatment arms, there will be no pooling of analysis arms.

Data collected with the intended use of efficacy analyses will be presented on the FAS. Safety analyses will be based on the SAS.

12.2 Trial Analysis Sets

Screening, screen failure data and trial analysis population sets will be presented as a listing.

12.3 Country and Site

This data will be presented as a listing.

12.4 Subject Disposition

Subject disposition will be presented as a listing.

12.5 Demographic and Baseline Characteristics

An overall summary of demographic and baseline characteristics will be presented by the four treatment arms, for the FAS population. The overall summary of demographics includes age, sex, race and ethnicity (demographic form), and weight group (<70 kg and ≥70). In addition, the following baseline characteristics will be presented; height (cm), weight (kg), BMI, status of tobacco consumption (current, former, never)), alcohol use (substance use – alcohol form; does the subject consume alcohol?).

Demographic and baseline characteristics data will be listed as well.

12.5.1 Psoriasis History

Psoriasis history will be presented as a listing.

12.6 Medical History and Trial Disease History

Medical history and trial disease history data will be presented as listings.

12.7 Prior and Concomitant Medications

The data will be listed in a combined listing with concomitant and prior medications flagged.

12.8 Protocol Deviations

Protocol deviations will be presented as a listing.

12.9 Treatments

12.9.1 IMP Exposure and Compliance

Exposure to IMP will be tabulated by treatment arm for FAS including subjects receiving at least 1 planned injection, total number of planned injections administered, total number of actual injections administered, and exposure in years. The output will be presented for the entire treatment phase for the brodalumab, and the ustekinumab treatment arms.

Exposure to IMP and compliance to IMP schedule will be listed (IMP administration and compliance form) by treatment arm and visit.

IMP dispense and return (IMP dispense and return form) will be listed as well.

12.9.2 Vaccine Administration

Vaccine Administration data will be presented as a listing.

12.10 Efficacy Summaries

All efficacy summaries will be based on FAS.

12.10.1 Descriptive Analysis of Efficacy Endpoint Data

PASI endpoint data will be summarised descriptively (number of subjects (n), mean, standard deviation (SD), median, lower and upper quartiles (Q1 and Q3), minimum, and maximum) by time point and for the four treatment arms brodalumab, ustekinumab, placebo + brodalumab, and placebo + ustekinumab. The data will be presented without any handling of missing observations or imputation.

The following efficacy parameters will be listed as well.

- PASI Raw
- PASI Score
- sPGA
- CDLQI
- Itch Severity Assessment
- Itch-Related Sleep Assessment

12.11 Safety Analyses

The safety analysis will be based on the safety analysis set.

12.11.1 Adverse Events

Outputs of occurrence of AEs will present number of subjects reporting the event, percentage of subjects reporting the event and number of events.

The AE (Adverse Event Form) tabulations is presented for TEAEs while in trial.

The following AE outputs will be presented:

- Overall summary of treatment-emergent AEs: any AE, any severe AE, any AE related to IMP, any severe AE related to IMP, any AE related to vaccine, any severe AE related to vaccine, any AE with outcome death, any SAE, any SAE related to IMP, any SAE related to vaccine, any AESI, any AE leading to withdrawal from trial, any AE leading to discontinuation of IMP

- All AE outputs will be presented by SOC and PT:
    - Occurrence of TEAEs
    - Occurrence of IMP related TEAEs
    - Occurrence of Serious TEAEs

The following listings will be presented. The listings will include all data collected as adverse events, including any adverse event occurring outside the definition for TEAEs will be flagged:

- Adverse Events (will include all AEs regardless if treatment emergent or not)
- Serious adverse events
- Adverse events of special interest

Adverse events will be coded using the most up to date version of the MedDRA dictionary. Current dictionary version will be documented in Data Management Plan.

12.11.2 Medication Error, Misuse and Abuse of IMP

This data will be presented as a listing.

12.11.3 Laboratory Data

Summaries of laboratory parameters (external vendor data) will be presented.

Chemistry and haematology parameters will be summarised by visit and treatment arm. Mean, standard deviation, median, Q1, Q3, minimum and maximum values be presented

The following listings will be presented:

- Chemistry and haematology parameters
- Serology parameters
- Urinalysis parameters
- Serum pregnancy test results
- Tuberculosis test results

Values outside the normal ranges will be flagged as applicable.

12.11.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The following summary will be presented: Number and percentages of subjects with the most severe C-SSRS response (defined in Appendix 1 Calculation of Scores) observed for each subject for the overall overall treatment phase by treatment arm.

The collected C-SSRS responses (ePRO) will be listed as well.

12.11.5 Patient Health Questionnaire-A (PHQ-A)

Number and percentages of subjects with the most severe total score based on PHQ-A response.

The categories defined in Appendix 1 Calculation of Scores will be used.

The collected PHQ-A responses (ePRO) will be listed as well.

12.11.6 Vital Signs

Vital signs parameters (systolic, diastolic blood pressure, pulse, and temperature) from the vital signs form will be presented by visit and following treatment arms: brodalumab, ustekinumab, placebo - brodalumab, and placebo - ustekinumab for the treatment phase. The vital signs will be summarised (mean, SD, median, Q1, Q3, minimum and maximum). Temperature will be presented in Celsius.

Vital sign parameters as detailed above will be listed.

12.11.7 Physical Examinations

The following variables will be listed from the Physical examination form: Was the physical examination performed? Reason if no, Results by visit.

13.0 References

Not Applicable

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse Events of Special Interest
ATC	Anatomic Therapeutic Classification
aTTA	Anti-tetanus toxoid antibodies
BMI	Body Mass Index
CDLQI	Children's Dermatology Life Quality Index
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ePRO	electronic Patient Recorded Outcomes
FAS	Full Analysis Set
FDLQI	Family Dermatology Life Quality Index
IMP	Investigational Medicinal Product
IRT	Interactive Response Tool
IVRS	Interactive Voice Response System
MACE	Major Adverse Cardiac Events
NRS	Numeric Rating Scale
PASI	Psoriasis Area Severity Score
PHQ	Patient Health Questionnaire
PK	Pharmacokinetic
PP	Per Protocol
PSO	Predictive Study Operations
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
SIB	Suicidal Ideation and Behaviour
sPGA	static Physicians Global Assessment

TEAE	Treatment Emergent Adverse Events

Appendix 1 Calculation of Scores

In this section examples of score calculations will be given

PASI Score

Body region	Redness (erythema)	Thickness (induration)	Scaliness (desquamation)	Sum of severity scores	Area Score	Weighting factor	Body Region Score
Head and neck	0	0	0	0	0	0.1	0
Trunk	2	3	1	6	2	0.3	3.6
Upper extremities	2	2	1	5	3	0.2	3
Lower extremities	2	2	1	5	1	0.4	2
This is a numeric example to demonstrate the PASI calculation. The PASI score is the sum of the 4 body region scores (each calculated as SSS ($SS_{Redness}$ + $SS_{Thickness}$ + $SS_{Scaliness}$) x AS x Weighting factor)							8.6 (Range 0-72)

Abbreviations: AS, area score; PASI, Psoriasis Area and Severity Index; SS, severity score; SSS, sum of severity scores.

CDLQI and FDLQI

The total score is calculated by summing the score of each question, resulting in a maximum of 30 and a minimum of 0.

sPGA

The score is given between 0 and 5.

C-SSRS

The severity of the response will be ranked in the following order from least to most severe:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods (not plan) without intent to act
4. Active suicidal ideation with some intent to act, without specific plan
5. Active suicidal ideation with specific plan and intent
6. Preparatory acts or behaviour
7. Aborted attempt
8. Interrupted attempt
9. Actual attempt (non-fatal)
10. Completed suicide

PHQ-A

For summaries of PHQ-A total scores the following categories will be used:

- 0-4 (none - minimal)
- 5-9 (mild)
- 10-14 (moderate)
- 15-19 (moderately severe)
- 20-24 (severe)

Definition of Weekly Average Itch Score (Adolescent Pruritus NRS and Itch-related Sleep NRS

Assessments recorded on Day 1 through Day 7 will be used to calculate the average for Week 1, and assessments on Day 8 through Day 14 for week 2, until the end of the last week itching is recorded. A minimum of the 4 out of the 7 planned assessments must be recorded, if this not the case for any given week, the value of the average weekly itch will be set to missing.

The baseline average weekly itch assessments will be based on the assessments recorded between Day -6 and the assessment closest to last pre-dose date. The daily itch assessments used to calculate the average weekly itch severity and itch-related sleep loss will be anchored to the date of randomisation. For example, assessments recorded on Day 1 through Day 7 will be used to calculate the average itch during week 1, assessments recorded on Day 8 through Day 14 will be used to calculate the average itch during week 2, etc. In order to assess the average weekly itch severity/itch-related sleep loss, a minimum of 4 out of the 7 planned assessments must be recorded. Otherwise, the average weekly itch severity/itch-related sleep loss score will be considered missing.