NOVARTIS

Clinical Development

CAIN457A/METABOLYX

CAIN457ADE08 / NCT03440736

A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period

Statistical Analysis Plan (SAP), Addendum 1.0

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19-Sep-2022	After Final DB lock	Creation of Addendum version 1.0	Text modified in section 2.9.1	2.9.1

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
CDBL	Clinical Database lock
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study report
ENR	Enrolled Set
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HbA1c	Hemoglobin A1c
HDL	High-Density Lipoprotein
hsCRP	high-sensitivity C-reactive Protein
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model for Repeated measures
PLS	Product Lifecycle Services
PRO	Patient-reported Outcomes
QoL	Quality of Life
RAN	Randomized Set
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TB	Tuberculosis
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis as planned in section 9 in the clinical study protocol version 00 for the clinical trial CAIN457ADE08 (METABOLYX). Additional analyses, specifications or deviations from the study protocol planned before database lock will also be discussed in this SAP.

1.1 Study design

This study is designed as a randomized, open-label, parallel-group, active comparator-controlled trial with two treatment arms. The design is shown in Figure 1-1.

Figure 1-1 Study Design

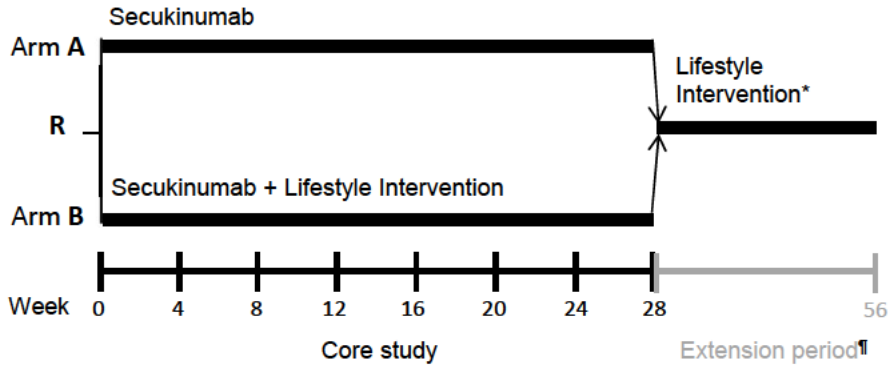

Fig. 1-1: Study Design: **R** Randomization, * During the extension period the lifestyle intervention can be continued by patients who have been in arm B during the core study or it can be started by patients who have been in arm A. Participation in the lifestyle intervention during the extension period is **not** mandatory. ¶Participation in the extension period itself is mandatory. Psoriasis treatment during the extension period can be chosen freely by the Investigator. No study drug is supplied during the extension period.

Core study: After providing informed consent patients will be screened for eligibility for a period of 1-4 weeks prior to inclusion into the study. If eligible, patients will then be randomized to one of the two treatment arms, which are the following:

- **Arm A**: Patients in arm A receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28, where they complete the core study. The last Secukinumab injection is performed at week 24.
- **Arm B**: Patients in arm B receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28. The last Secukinumab injection is performed at week 24. **In addition to Secukinumab treatment patients in arm B participate in a lifestyle intervention program**.

The core study ends at week 28.

Extension period: After 28 weeks the study continues with an extension period, during which lifestyle intervention is offered to all patients, irrespective of their prior treatment arm. This means that patients of arm B, who are willing to, can continue their previously started lifestyle intervention program and patients of arm A, who are willing to, can start the lifestyle intervention program at the beginning of the extension period. **All patients, irrespective of their decision whether to start/ continue lifestyle intervention or not, have to participate in the extension period and visit their dermatologic study center for scheduled visits**. The extension period ends at week 56, where all patients complete the study. There will be no study drug supply during the extension period. The treating physician can chose psoriasis therapy freely according to his discretion.

1.2 Study objectives and endpoints

The study objectives and endpoints are described in Table 1-1

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
Primary Objective	**Endpoints for primary objective**
1. To demonstrate that the combination of Secukinumab (300 mg, 4-weekly s.c.) with lifestyle intervention results in higher psoriasis treatment efficacy than Secukinumab alone in psoriasis patients with concomitant metabolic syndrome	1. Percentage of patients achieving PASI90 at week 28 in both randomized treatment arms, Secukinumab alone and Secukinumab combined with lifestyle intervention
Secondary Objectives	**Endpoints for secondary objectives**
1. To explore treatment efficacy of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone	1. PASI75, 90 and 100 as well as absolute PASI scores in both treatment arms at week 1, 2, 3, 4, 8, 12, 16, 20, 24 and 28
2. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on systemic inflammation	2. hsCRP in both treatment arms throughout the duration of the core study
3. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to	3. HbA1c, fructosamine and fasting plasma glucose in both treatment arms throughout the duration of the core study

Objectives	Endpoints
Secukinumab alone on glucose metabolism	
4. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on lipid metabolism	4. Total cholesterol, LDL, HDL and triglycerides in both treatment arms throughout the duration of the core study
5. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on body weight and waist circumference	5. Waist circumference (cm), body weight (kg) and BMI (kg/m^2) in both treatment arms throughout the duration of the core study
6. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on systolic and diastolic blood pressure	6. Systolic and diastolic blood pressure (mmHg) in both treatment arms throughout the duration of the core study
7. To evaluate the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on health-related quality of life, itch, pain and scaling as well as mental well-being	7. Absolute DLQI, relative change of DLQI, proportion of patients with DLQI 0/1, absolute WHO-5, relative change in WHO-5, absolute self-assessed itch, pain, scaling, relative change in self-assessed itch, pain, scaling in both treatment arms throughout the duration of the core study

Objectives	Endpoints
[redacted]	
5. To explore the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on biomarkers including but not limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis/steatosis, heart injury, as well as to inflammatory processes in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with secukinumab alone)	5. At baseline (week 0), week 16 and week 28 the following markers will be assessed: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

All statistical analysis will be performed by Novartis Product Lifecycle Services (PLS). Data will be analyzed by statistical software SAS version 9.4 according to the data analysis section 9 of the study protocol.

2.1.1 General definitions

Summary statistics for continuous variables will include N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, standard deviation (SD), median, minimum & maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed.

If not otherwise specified, p-values will be presented as two-sided p-values along with the two sided confidence interval.

Unless otherwise stated, the level of significance will be set to 5% (two-sided).

Change from baseline and percentage change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated wherever applicable as:

Change from baseline = post-baseline value – baseline value.

Percentage change from baseline= ((Change from baseline value)/ (baseline value))*100

2.1.1.1 Study Treatment and Study Day

The day of randomization visit where the patients were allocated to their respective treatment arm i.e. Arm A or Arm B, respectively is defined as Day 1. All study days will be labelled relative to Day 1. Day 0 will not be used, the day before Day 1 is Day -1.

For events occurring on or after Day 1,

Study day=[Date of event]-[Date of first dose] + 1

For events occurring prior to Day 1,

Study day=[Date of event]-[Date of first dose]

2.1.1.2 Screening, baseline and post-baseline definitions

Screening period refers to the period starting from signing the informed consent until randomization or screening failure. Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment.

For efficacy analyses, baseline is the last available pre-dose assessment obtained at Visit 2. If the measurements at Visit 2 are missing then the measurements obtained at Visit 1 will be considered as the baseline. All assessments obtained after Visit 2, are considered as post-baseline.

For safety analyses, baseline is the last assessment obtained before the first dose of study treatment i.e. Secukinumab, is Visit 2. If the measurements at Visit 2 are missing then the measurement at Visit 1 will be considered as the baseline. All assessments obtained after the first dose of study treatment i.e. Secukinumab, are considered as post-baseline.

2.2 Analysis sets

The following analysis sets will be used for the data analysis.

Enrolled Set (ENR): The ENR will consist of all patients who provided signed and dated informed consent

Randomized Set (RAN): The RAN will consist of all patients who were randomized into this study at baseline. Patients in the RAN will be analyzed according to the treatment they were randomized to.

Safety Set (SAF): The SAF will consist of all patients who received at least one dose of study treatment i.e. Secukinumab. Patients will be analyzed according to the treatment they received, i.e. secukinumab alone or Secukinumab with life-style intervention.

Full Analysis Set (FAS): The FAS will consist of all patients who were randomized into this study at Baseline and received at least one dose of study treatment i.e. Secukinumab. Following the intent-to-treat principle, patients in the FAS will be analyzed according to the treatment assigned at randomization.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of patients screened will be presented along with the reasons for screen failures for all the subjects in the ENR dataset. The number and percentage of patients screened, screen failures, randomized, completed or discontinued from the study (i.e. using baseline disposition CRF and treatment period disposition CRF), including reasons for discontinuation will be presented by treatment group for all patients in the ENR dataset. Patients who screen-failed and

were re-screened under a new patient number will have earlier screening numbers collected on the re-screening CRF. Patients will be counted once in the total number of screenings.

The number and percentage of patients with major protocol deviations (see Section 5.3) will be tabulated by category and deviation in the RAN dataset. Protocol deviations will be listed with date, study day of occurrence, deviation and severity codes.

Moreover, a patient flow diagram of the ENR population will be presented in accordance with the CONSORT guidelines (http://www.consort-statement.org/). Demographics and other baseline characteristics

Descriptive statistics for the background and demographic data will be provided for the FAS dataset. Continuous variables will be summarized using N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, median, standard deviation, minimum and maximum.

Frequency counts and percentages will be presented for categorical variables for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed. Two-sided 95% Confidence intervals will be evaluated and reported for frequency percentages using clopper-pearson / Exact method.

2.3.1.1 Demographic and background characteristics

The following data will be summarized:

- age (in years, and year categories ≤ 65, > 65)
- gender (male/female)
- child bearing status (able to bear children/post-menopausal/sterile - of child bearing age)
- race (Asian/Caucasian/Black or African American/Unknown/Other)
- source of subject referral
- smoking status (never/current/former)
- average pack year (former/current/overall)
- height (cm)
- weight (kg)
- body mass index (BMI) = weight (kg) / (height (meters))^2
- waist circumference (cm)
- hip circumference (cm)
- waist to hip ratio = waist circumference (cm)/ hip circumference (cm)
- sitting pulse (bpm)
- systolic and diastolic blood pressure (mmHg)
- serum pregnancy test (negative/positive)

2.3.1.2 History of previous psoriasis treatments

The following medical history and prior treatments captured at Visit 1 will also be summarized for the FAS dataset.

1. The occurrence (yes/no/unknown), status at start of study (ongoing - no/yes) and duration (in years) of cardiovascular diseases by medical history term
2. The occurrence (yes/no), status at start of study (active or ongoing - no/yes) and duration (in years) of plaque-type, nail, scalp, palms and soles
3. The occurrence (yes/no), (ongoing – no/yes), type (if ongoing), and duration (in years) of psoriatic arthritis
4. The occurrence of prior psoriasis therapy including name of therapy/medication, type of therapy, type of psoriasis treated, total number of months of exposure and reason for discontinuation.

Duration (in years) of disease is calculated as (Visit 1 date – date of first diagnosis of disease + 1)/365.25.

All prior medications will be summarized by Anatomic Therapeutic Chemical (ATC) class and PT according to the World Health Organization (WHO) Drug Reference List dictionary (version 201909 or higher). The ATC class will be presented in alphabetical order. Preferred terms will be sorted by decreasing proportion and alphabetical order.

2.3.1.3 Medical history and current medical condition

Relevant medical history and current medical conditions (other than psoriasis, psoriatic arthritis, and cardiovascular diseases) present prior to signing of the informed consent and until the start of study treatment i.e. secukinumab, will be presented by primary system organ class (SOC) and preferred term (PT). coded using the Medical Dictionary for Regulatory Activities terminology (MedDRA version 20.1 or higher).

Medical Histories/conditions will be summarized for the FAS set (displaying totals) coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology version 22.1 or higher. The primary SOCs will be presented in alphabetical order. Preferred terms will be sorted by decreasing proportion and alphabetical order.

The tuberculosis (TB) assessment result (active TB, latent TB and no TB) will be summarized (displaying totals) as part of medical history. TB assessment details as collected on the TB assessment CRF will be listed separately for the FAS set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment

The number and percentage (%) of patients receiving injections will be summarized categorically (one less then all, two less then all etc.) for the core study using the SAF set by

treatment groups and overall. The duration of exposure (days) to secukinumab study treatment will be presented similarly.

[Duration of exposure is calculated as (last known date of study medication (as per the DAR CRF) – start date of medication) + 1] / 7 (in weeks)

The duration of exposure will be reported in weeks.

Start date and last known date of study medication will be as per the drug accountability record eCRF page.

2.4.2 Study compliance

2.4.2.1 Secukinumab

Compliance as percentage of injections administered will be calculated as the number of injections applied (based on documented study drug administrations and syringe counts as given in the dosage administration record eCRF page) divided by the number of injections scheduled per protocol. It is to be noted that for dropouts/discontinuations, the denominator will be adjusted to number of injections scheduled per protocol until discontinuation.

It is given by the formula:

Compliance (%) = 100*(total no of injections administered) / (no. of injections prescribed untill discontinuation)

In the core study selection phase Secukinumab 300 mg, two autoinjectors containing 150 mg Secukinumab, will be provided as open label medication at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 (last injection is at week 24).

Compliance percentage will be summarized for the SAF dataset (displaying totals) by treatment group and also by categories (< 80% and ≥ 80% to 100%).

2.4.2.2 Lifestyle intervention

Compliance as percentage of lifestyle intervention visits participated in will be calculated as the number of intervention visits attended (based on documented participation counts as given in the lifestyle intervention record eCRF page) divided by the number of lifestyle intervention visits scheduled per protocol until discontinuation. It is to be noted that for dropouts/discontinuations, the denominator will be adjusted to number of intervention visits participated scheduled per protocol until discontinuation.

It is given by the formula:

Compliance (%) = 100*(total no of lifestyle intervention visits participated) / (no. of lifestyle intervention visits scheduled)

In the core study selection phase lifestyle intervention visit are scheduled at weeks 0, 1, 2, 3, 4, 8, 16 and 24. In the extension study phase the visits are scheduled for weeks 36, 44 and 56. Patients in Arm A starting lifestyle intervention during the extension phase will have their first

lifestyle intervention at week 28. Patients in Arm A do not have a lifestyle intervention at week 56. Patients in Arm B have lifestyle intervention visits at E1, E2 and E3.

Compliance percentage will be summarized for the SAF dataset (displaying totals) by treatment group and also by categories (< 80% and ≥ 80% to 100%).

2.4.3 Prior, concomitant and post therapies

Prior and concomitant medications along with non-drug therapies will be summarized using the SAF set by treatment group, separately.

Prior medications are defined as treatments taken and stopped prior to first dose of secukinumab study treatment. Any medication given at least once between the day of first dose of secukinumab study treatment and the last day of study visit will be a concomitant medication, including those which were started pre-baseline and continued into the treatment period.

Medications will be presented in order of frequency, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Preferred terms will be sorted by decreasing proportion and alphabetical order.

Tables will also show the overall number and percentage of subjects receiving at least one treatment in a particular ATC code.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary variable is the percentage of patients achieving PASI90 at week 28 in both randomized treatment arms, Secukinumab alone and Secukinumab combined with lifestyle intervention.

The primary analysis will be to demonstrate that the combination of Secukinumab (300 mg, 4-weekly s.c.) with lifestyle intervention results in higher psoriasis treatment efficacy than Secukinumab alone with respect to the primary endpoint in the FAS.

PASI score will be derived as indicated in Table 2-1. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details to help with the assessment are provided below:

1. The neck is assessed as part of the head
2. The axillae and groin are assessed as part of the trunk
3. The buttocks are assessed as part of the lower limbs
4. When scoring the severity of erythema, scales should not be removed

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the formula:

$PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L$

The keys for the letters are provided in Table 2-1.

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The baseline value for analysis of the PASI is collected at the Randomization Visit.

Table 2-1 The PASI scoring system

Body Region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head(H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=>10-<30% 3=>30-<50% 4=>50-<70% 5=>70-<90% 6=>90-100%
Trunk(T)‡	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=>10-<30% 3=>30-<50% 4=>50-<70% 5=>70-<90% 6=>90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=>10-<30% 3=>30-<50% 4=>50-<70% 5=>70-<90% 6=>90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=>10-<30% 3=>30-<50% 4=>50-<70% 5=>70-<90%

Body Region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
				6=>90-100%

*Percentage (not score) of body region (not whole body) affected will be entered in the eCRF †Neck is assessed as part of the Head (H) body region

‡Axillae and groin are assessed as part of the Trunk (T) body region

§Buttocks are assessed as part of the Lower limbs (L) body region

Definitions of efficacy variables based on PASI

The following definitions will be used in this study:

- **PASI 50 response:** subjects achieving ≥50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders
- **PASI 75 response**: subjects achieving ≥75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response / remission**: complete clearing of psoriasis (PASI=0)

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis to be rejected is that the odds of response Week 28 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 28 are higher under Secukinumab combined with lifestyle intervention compared to Secukinumab alone.

Let p_j denote the proportion of responders at Week 28 for treatment group j, j=0, 1, where

- 0 corresponds to Secukinumab combined with lifestyle intervention
- 1 corresponds to Secukinumab alone

The following hypotheses will be tested:

$$H_0: (p_1 / (1- p_1)) / (p_0 / (1- p_0)) = 1 \text{ versus } H_A: (p_1 / (1- p_1)) / (p_0 / (1- p_0)) \neq 1$$

In other words:

H_A: The odds ratio of achieving a response at Week 28 for Secukinumab combined with lifestyle intervention vs Secukinumab alone is different from 1.

The primary analysis will be performed on FAS dataset comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, center and covariate baseline PASI. The odds ratio and its 95% confidence interval (CI) and p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the

logistic regression model for the factor "treatment" is < 0.05; however, superiority of Secukinumab combined with lifestyle intervention will be claimed only if the direction is correct, i.e. if the odds of response are larger under Secukinumab combined with lifestyle intervention.

2.5.3 Handling of missing values/censoring/discontinuations

Patients who do not have a valid PASI assessment at week 28 will be regarded as non-responders for the primary analysis.

2.5.4 Sensitivity analyses

The primary endpoint will be analyzed by means of a Cochran-Mantel-Haenszel (CMH) test using the FAS set. This test will be stratified by center. Treatment groups will be compared with respect to the proportion of responders using the CMH test statistics. The corresponding p-values will be based on the CMH statistics which follows a Chi-square distribution with one degree of freedom.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Analysis of secondary endpoints

PASI 75, 90 and 100 at weeks 1, 2, 3, 4, 8, 12, 16, 20, 24 and 28 will be analyzed analogous to the primary endpoint. Absolute PASI scores will be analyzed using a MMRM, with factors treatment, center, visit, visit*treatment interaction and covariate baseline PASI. The raw as well as the adjusted least squares means and their differences between treatment groups will be calculated for each visit together with their corresponding 95% confidence intervals and p-values.

The same MMRM model updated with relevant baseline covariate similar to primary endpoint will also be used for the analyses of the other continuous secondary endpoints hsCRP, HbA1c, fructosamine, fasting plasma glucose, LDL, HDL, total cholesterol, triglycerides, waist circumference, BMI, body weight, systolic and diastolic blood pressure, QoL-scores (Absolute DLQI total score, relative change from baseline of DLQI total score, absolute WHO-5 total score, relative change from baseline in WHO-5 total score, absolute self-assessed itch, pain, and scaling, relative change from baseline in self-assessed itch, pain, and scaling) and activity levels (steps per day).

All the patients reporting DLQI score = 0 or 1 will be considered as "Responders (0)", whereas the patients reporting DLQI score ≥ 2 will be considered as "Non-responders (1)".

Proportion of patients with DLQI score (0&1) i.e., DLQI responders will be evaluated in both the arms and will be compared using a logistic regression model with the factors treatment, center, visit, visit*treatment interaction and covariate baseline DLQI. The odds ratio and its 95% confidence interval (CI) and p-value will be reported. See Appendix 5.3 for more details on PROs.

Note: For the subjects with fasting & non-fasting status, separate analyses will be performed for fasting plasma glucose, fructosamine, and HbA1c levels.

2.6.2 Handling of missing values/censoring/discontinuations

Non-responder imputation will also be applied to all secondary response variables. For continuous secondary endpoints, all available measurements will be included in the Mixed Model for Repeated Measures (MMRM).

[redacted]

2.7.5 Effect of Secukinumab combined with lifestyle intervention on a biomarker sub-study

A biomarker sub-study will be performed during the core study to explore the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on biomarkers in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with Secukinumab alone).
At baseline (week 0), week 16 and week 28 the following markers will be assessed using fasting blood samples: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel. All endpoints of the biomarker sub-study will be summarized by visit and analyzed using the same MMRM model as described in section 2.6.1.
Only patients participating in the biomarker sub-study will be considered for this analysis. As the biomarker sub-study is planned to be conducted for the biomarkers samples collected under fasting conditions, so the subjects with non-fasting status will be analysed separately and independently.

2.8 Additional analysis

In order to explore the additional effect of lifestyle intervention on various related end-points an additional analysis will be performed for PASI 75, PASI 90 & PASI 100 and all the study biomarkers at V9 (Week 16), V12 (Week 28) and end-of-study i.e. Week 56 for both treatment arms, separately based on three below mentioned subgroups:

- Patients with weight loss <5%
- Patients with weight loss ≥ 5% - < 10%
- Patients with weight loss ≥ 10%

For all the above mentioned sub-groups no. of patients falling in each sub-group will be descriptevely summarized using frequency, percentages and exact 95% clopper-pearson CI at V9 (Week 16), V12 (Week 28) and end-of-study i.e. Week 56 for both treatment arms, separately using FAS. Change in weight loss will be compared from the baseline weight.

All the patients who achieved PASI 75, 90 & 100 at V9 (Week 16), V12 (Week 28) and end-of-study i.e. Week 56 will be descriptevely summarized uing frequency, percentages and exact 95% CI using clopper-pearson method for the above mentioned sub-groups in both treatment arms, separately using FAS. Further additional analysis will be performed on FAS dataset comparing treatments with respect to the PASI 75, 90 & 100 in a logistic regression model with the factors treatment, center and covariate baseline PASI. The odds ratio and its 95% confidence interval (CI) and p-value will be given. The above analysis will be performed for all the three sub-groups independentally.

PASI score at baseline & PASI 75, 90 & 100 scores and biomarkers value will be descriptevely summarized using N, n, Mean, median, standarad deviation, min, max for all the three subgroups using FAS. All the summary statistics and analysis on biomarkers will be performed

only for the patients participating in Biomarker substudy. Further, PASI 75, 90 and 100 scores at V9 (Week 16), V12 (Week 28) and end-of-study i.e. Week 56 will be analyzed for all the three sub-groups, separately. Absolute PASI scores will be analyzed using a Mixed Model for Repeated Measurements (MMRM) with factors treatment, center, visit, visit*treatment interaction and covariate baseline PASI. The raw- as well as the adjusted (LS-) means and their differences between treatment groups will be calculated for each visit together with their corresponding 95% confidence intervals and p-values, for all the three sub-groups separately. Also, similar MMRM model will be used for the biomarkers Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel for all the three sub-groups, separately.

All the above mentioned analysis for PASI 75, 90, 100 & all study biomarkers will be performed separately for both treatment groups for below mentioned comparisons:

a. Patients with weight loss ≥ 5% - < 10% vs. Patients with weight loss <5%
b. Patients with weight loss ≥ 10% vs. Patients with weight loss <5%

2.9 Safety analyses

All safety analyses will be based on the SAF set.

2.9.1 Adverse events

Treatment emergent adverse events (events started after the first dose of secukinumab study treatment or events present prior to the first dose of secukinumab study treatment but increased in severity) will be summarized by preferred term up to 28 weeks after the first dose..

AEs will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class (SOC) and having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for secukinumab study treatment (with and without life-style intervention) related AEs. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable. Furthermore, a listing of all adverse events, including SAE, will be provided. SAEs will be summarized.

Separate summaries will be provided for death, SAE, other significant AEs leading to secukinumab study treatment (with and without life-style intervention) discontinuation and AEs leading to dose adjustment (including secukinumab study treatment discontinuation).

Deaths occurring after signing of informed consent and prior to the start of the core study will be presented in the listing.

2.9.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry and urinalysis). All the laboratory parameters and biomarkers with values below and above the limit of quantification (LOQ) will be reported as LOQ/2. Descriptive summary statistics for the change from Baseline to each study visit will be presented.

These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from Baseline will only be summarized for patients with both Baseline and Post-Baseline assessments.

Change from baseline = post-baseline value – baseline value

For each parameter, the maximum change from Baseline within each study period will be analyzed analogously.

Below mentioned laboratory parameters will be descriptively summarized. Frequencies and percentages will be presented for patients with clinically notable laboratory value, for below mentioned selected lab parameters:

Clinically notable laboratory values

Liver Function and Related Variables

- ALT (SGPT): > 3 x Upper Limit of Normal (ULN)
- AST (SGOT): > 3 x ULN
- Total bilirubin: > 1.5 x ULN
- Alkaline phosphatase: > 2 x ULN

Renal Function and Electrolyte Variables

- Creatinine (serum): > 1.5 x ULN

Hematology Variables

- Hemoglobin: ≥ 20 g/dL decrease from baseline
- Platelet count: < Lower Limit of Normal (LLN)
- White blood cell count: < 0.8 x LLN
- Neutrophils: < 0.9 x LLN
- Eosinophils: > 1.1 x ULN
- Lymphocytes: > 1.1 x ULN

Clinically significant abnormal laboratory values will also be summarized for the following parameters of the biomarker sub-study: Adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, NT-proBNP. Only patients participating in the biomarker sub-study will be included.

2.9.3 Other safety data

2.9.3.1 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from Baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from Baseline will only be summarized for patients with both Baseline and post-baseline values. Vital signs included are: weight (kg), BMI = weight (kg) / (height at visit 1 (meters))^2, waist circumference (cm), hip circumference (cm), waist to hip ratio = waist, circumference (cm)/ hip circumference (cm), sitting pulse (bpm), systolic and diastolic blood pressure (mmHg).

2.10 Patient-reported outcomes

See Section 5.2

2.11 Interim analysis

A first analysis of the core study (primary, secondary [redacted] endpoints related to the core study) will be performed after all subjects have completed the core study.

[redacted]

The two analyses will be reported in separate clinical study reports.

3 Sample size calculation

This study is primarily designed to demonstrate superiority of secukinumab combined with lifestyle intervention vs Secukinumab alone in terms of PASI90 response at week 28. A PASI90 response of 81% at week 28 under Secukinumab alone in patients with metabolic syndrome is assumed. This number is based on a retrospective analysis performed with data from the CLEAR study, taking into account the slightly higher BMI of the patient population with metabolic syndrome (BMI 23-42 kg/m^2, Albareda M et al., 2014) and the open-label design.

Evidence on effect size of lifestyle intervention on PASI response is relatively rare and assumptions were based on the following studies: A clinical study by Al-Mutairi et al (2014) showed an absolute increase of 27% in PASI75 response to biologic treatment (Infliximab, Etanercept, Ustekinumab, Adalimumab) in overweight or obese, moderate to severe psoriasis patients undergoing weight reduction compared to patients not undergoing weight reduction. However the dietary regimen used in this study was highly restrictive and consecutively led to a strong mean weight loss (-13 kg vs + 1,5 kg in the control group after 24 weeks). Naldi et al (2014) showed an absolute increase of 6% in PASI75 response to systemic treatment in overweight to obese, moderate to severe psoriasis patients undergoing diet and physical exercise compared to control patients. The lifestyle intervention in this study was less intensive and consecutively led to a smaller mean weight loss (-3kg vs -1.6 kg in the control group after 20 weeks). It seems that the extent of increase in PASI response correlates with the achieved weight loss, at least to a certain extent. PASI90 data were not available for both cited studies. The lifestyle intervention conducted in the present study is less intensive than the one applied by Al-Mutairi et al. but more intensive compared to Naldi et al. A lifestyle intervention very similar to the one applied in our study was previously able to show a mean weight loss of -3.8 kg vs. -1.4 kg after 1 year (Kulzer B et al., 2014). Maximum weight loss can already be expected after 3-4 month. As part of the lifestyle intervention program activity tracking devices will be used in the present study to further support the lifestyle intervention.

Based on these considerations and the fact that we are looking at PASI90 response in the present study, we assume an absolute increase of 9% in PASI90 response in the Secukinumab combined with lifestyle intervention arm to 90% PASI90 responders compared to 81% PASI90 responders in the Secukinumab alone arm. An absolute increase of 9% in PASI90 responders would also be clinically meaningful.

Based on these assumptions 342 patients per arm would provide a power of 90 % at a two-sided alpha of 0.05 to demonstrate that the percentage of PASI90 responders at week 28 is higher in the Secukinumab combined with lifestyle intervention arm compared to the Secukinumab alone arm. In case the true effect size would only be 7.5 %, this sample size would still provide a power of 75 %. To compensate for some expected drop out and/or premature discontinuations, 380 patients per arm are planned to be recruited for this study.

4 Change to protocol specified analyses

Below mentioned changes to the analysis described in Section 9 of the protocol version 02 are planned.

i. Separate analyses will be performed for subjects with fasting and non-fasting status for fasting plasma glucose, fructosamine, and HbA1c in secondary analyses

ii. Separate analyses will be performed for subjects with fasting and non-fasting status for all the biomarkers in biomarker sub-study

iii. Additional analysis proposed for stratification of the analysis for PASI 75, PASI 90, PASI 100 and all study biomarkers by the groups “patients achieving weight loss < 5%”, “patients achieving weight loss ≥ 5% - < 10%” and “patients achieving weight loss ≥ 10%” in each treatment arm.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, 31DECYYYY, date of death.
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, last day of the month, date of death.
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.1.2 AE start date

AEs with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment within this study.

Partial AE start dates are imputed with reference to the first administration of study treatment within this study as outlined in the table below.

The date value is split into day, month, year sections and referenced in the imputation table as outlined below.

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Treatment Start	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates AE start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates AE start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, Treatment Start +1)
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

Before imputing the AE start date, find the AE start reference date.

- If the AE end date is complete and the (imputed) AE end date < Treatment Start Date then AE start reference date = min (study informed consent date, earliest visit date).
- Else AE start reference date = Treatment Start Date

To impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the study treatment start date year value, the AE started before study treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the study treatment start date year value, the AE started after study treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the study treatment start date month or greater than the study treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date

To impute concomitant end date:

1. If the concomitant end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the concomitant end year value is missing or ongoing, the imputed concomitant end date is set to NULL.
2. Else, if the concomitant end date month is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, 31DECYYYY, date of death.
3. If the concomitant end date day is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, last day of the month, date of death.

If the imputed concomitant end date is less than the existing concomitant start date, use the concomitant start date as the imputed concomitant end date.

5.1.2.2 Concomitant medication start date

Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the first administration of study treatment within this study in accordance with the rules outlined below.

	Day	Month	Year
Partial Concomitant medication (CMD) Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(C) Uncertain	(A) = 15MONYYYY Before Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates CMD start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates CMD start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, Treatment Start Date +1)
(C) Uncertain	IF CMDTYP IN (1, 3) THEN Treatment Start Date -1

Relationship	
	ELSE IF CMDTYP IN (. 2) THEN Treatment Start Date +1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

To compute concomitant start date:

1. If the concomitant start date year value is missing, the imputed concomitant start date is set to one day prior to study treatment start date.
2. If the concomitant start date year value is less than the study treatment start date year value, the concomitant medication started before study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the mid-year point (01JULYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
3. If the concomitant start date year value is greater than the study treatment start date year value, the concomitant started after study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the year start point (01JANYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the month start point (01MONYYYY).
4. If the concomitant start date year value is equal to the study treatment start date year value:
   a. And the concomitant month is missing or the concomitant month is equal to the investigational treatment start date month, then the imputed concomitant start date is set to one day prior to investigational treatment start date.
   b. Else if the concomitant month is less than the investigational treatment start date month, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
   c. Else if the concomitant month is greater than the investigational treatment start date month, the imputed concomitant concomitant start date is set to the month start point (01MONYYYY).

If complete (imputed) concomitant end date is available and the imputed concomitant start date is greater than the (imputed) concomitant end date, then imputed concomitant start date should be set to the (imputed) concomitant end date.

5.1.3 Other imputations

Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If diagnosis year < study treatment start date year and diagnosis month is missing, the imputed diagnosis date is set to the mid-year point (01JULYYYY)

- Else if diagnosis month is not missing, the imputed diagnosis date is set to the mid-month point (15MONYYYY)
- If diagnosis year = study treatment start date year and (diagnosis month is missing OR diagnosis month is equal to study treatment start month), the imputed diagnosis date is set to one day before study treatment start date

5.2 Statistical models

5.2.1 Primary analysis

Logistic regression model

The proportions of patients who achieve a PASI 90 response at Week 28 for each treatment group will be compared using logistic regression analysis. The model will include treatment and center as fixed effect and with covariates PASI score at baseline (Visit 2).

The SAS procedure PROC GLIMMIX will be used with the following SAS code:

```
proc glimmix data=.... order=internal;
class trtn1 cntr ;
model response = trtn1 cntr basv2 / ddfm=kr error=binary
link=logit;
lsmeans trtn1 / cl diff oddsratio;
run;
```

where

response = PASI 90 response (= 1 or 0)

trtn1 = treatment

cntr = center

basv2 = PASI score at baseline (Visit 2)

The estimated odds ratios will be displayed along with the associated 95% confidence intervals and p-values (two-sided).

5.3 Patient reported outcomes (PRO)

PROs will be assessed by the following validated instruments.

• Dermatology Life Quality Index (DLQI©)
• Self-assessed pain, itching, scaling
• WHO-5

Dermatology Life Quality Index (DLQI©)

The DLQI© is a 10-item general dermatology disability index designed to assess Health-related quality of life (HRQoL) in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan, 1994; Basra et al., 2008).

The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 33 different skin conditions and is available in 85 languages. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The recall period is the previous week, and the instrument takes 1 to 2 minutes to complete.

Each item has four response categories including 0 (not at all), 1 (a little), 2 (a lot), and 3 (very much). "Not relevant" is also a valid response and is scored as 0.

The DLQI© total score is the sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI© may also be analyzed separately.

Meaning of DLQI Scores

- 0-1= no effect at all on subject's life
- 2-5= small effect on subject's life
- 6-10= moderate effect on subject's life
- 11-20= very large effect on subject's life
- 21-30= extremely large effect on subject's life

DLQI response 0/1 variable will be calculated based on the DLQI total score as follows:

- 0 – If DLQI total score is either 0 or 1
- 1 – If DLQI total score is > 1

DLQI percentage change from baseline will be calculated using DLQI total scores as follows:

((post-baseline total DLQI –baseline total DLQI)/ (baseline total DLQI))*100

Subject's self-assessed pain, itching and scaling

A self-administered, 11-point numeric rating scale (NRS, 0-10) will be used to evaluate the subject's assessment of their current pain, itching and scaling. Respondents will answer the following questions for the assessment of

- **Pain:** Overall, how severe was your psoriasis-related pain over the past 24 hours
- **Itching:** Overall, how severe was your psoriasis-related itch over the past 24 hours
- **Scaling:** Overall, how severe was your psoriasis-related scaling over the past 24 hours

Subjects have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e., no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (i.e., pain, itching or scaling as bad as it could be). The number that the patient selects represents his or her intensity score.

WHO-5

The 5-item World Health Organization Well-Being Index (WHO-5) is a validated, short questionnaire consisting of 5 simple questions, assessing subjective psychological well-being of the respondents. It is among the most widely used questionnaires for the assessment of psychological well-being and has been successfully applied across a wide range of study fields.

The measure is self-administered and takes approximately one minute to complete. The recall period is the previous two weeks. Each item has 6 response categories, ranging from 5 ("the whole time") to 0 ("at no time point"). The WHO-5 total score is the sum of the 5 questions. Each subscale of the WHO-5 may also be analyzed separately.

5.4 Major protocol deviations and other exclusion criteria

The following protocol deviations in FAS dataset will be considered and documented :

Protocol deviation ID	Deviation text description	Excluded from analysis set
INCL04D	If the DLQI at baseline is less than or equal to 10 or missing.	INCLUDE IN EVERYTHING
INCL04E	If Total BSA involvement affected by Paque type psoriasis at baseline is less than 10 or missing.	INCLUDE IN EVERYTHING
INCL05	Does not fulfill criteria to meet metabolic syndrome definition	INCLUDE IN EVERYTHING
EXCL02	Previous exposure to Secukinumab or any other biologic drug directly targeting IL17A or the IL17A receptor	INCLUDE IN EVERYTHING
EXCL03	Exposure to anti-TNF treatment during 1 year prior to baseline	INCLUDE IN EVERYTHING
EXCL06	History of latex hypersensitivity.	INCLUDE IN EVERYTHING
EXCL08A	Ongoing use of prohibited treatments.	INCLUDE IN EVERYTHING
EXCL08B	Administration of live vaccines 6 weeks prior to baseline (visit 2) or during the study period	INCLUDE IN EVERYTHING
EXCL10A	Patients with diagnosed un-controlled type 2 diabetes	INCLUDE IN EVERYTHING

EXCL10B	Patients treated with pharmacological therapy with Insulin, sulfonylurea agents/analogues, and/or thiazolidinediones/glitazones	INCLUDE IN EVERYTHING
EXCL13C	Serum pregnancy is missing or test not performed however the patient is randomised.	INCLUDE IN EVERYTHING
EXCL17A	Medical history of myocardial infarction	INCLUDE IN EVERYTHING
EXCL19	Serum creatinine level exceeding 2.0 mg/dl (176.8 µmol/L) at screening	INCLUDE IN EVERYTHING
EXCL20	Total white blood cell (WBC) count < 2,500/µl, or platelets < 100,000/µl or neutrophils < 1,500/µl or hemoglobin < 8.5 g/dl at screening	INCLUDE IN EVERYTHING
EXCL22B	History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive QuantiFERON TB-Gold test (QFT) misssing at screening	INCLUDE IN EVERYTHING
EXCL22E	Subject randomised with latent tuberculosis though appropriate treatment not initiated per local guidelines	
EXCL23	Past medical history record or current infection with HIV, hepatitis B or hepatitis C prior to baseline (visit 2).	INCLUDE IN EVERYTHING
EXCL24	History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or	INCLUDE IN EVERYTHING

	metastases (except for Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks prior to baseline (visit 2); carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).	
COMD01	Use of prohibited medication at any time during the traetment phase of study.	INCLUDE IN EVERYTHING
COMD02	Use of prohibited medication with potential impact on key efficacy and/or safety evaluations at any time during the study after randomization	INCLUDE IN EVERYTHING
COMD03	Use of prohibited medication not meeting the washout period requirement defined per protocol before baseline visit	INCLUDE IN EVERYTHING
TRT02	<2 injections of secukinumab administered by investigator	INCLUDE IN EVERYTHING
TRT04	More than 1 home administration by the subject.	INCLUDE IN EVERYTHING
TRT05	Subject randomised to arm B with no participation in Lifestyle intervention visit during core phase	INCLUDE IN EVERYTHING
TRT06	Missed visit-no drug administered	INCLUDE IN EVERYTHING
TRT07	First drug administration not at date of randomization/drug assignment date	INCLUDE IN EVERYTHING
TRT08	Patient has a 'Home administration' of study drug before visit 7	INCLUDE IN EVERYTHING
TRT10	Patient has been administered IMP at visit 12.	INCLUDE IN EVERYTHING
TRT11	Patient was administered secukinumab outside the study as commercial product instead of IMP prior to V12.	INCLUDE IN EVERYTHING

TRT12	No study drug administered	INCLUDE IN EVERYTHING
TRT13	Treatment not given due to COVID-19	INCLUDE IN EVERYTHING
TRT14	Patient has been administered expired Secukinumab	INCLUDE IN EVERYTHING
OTH06	Missing PASI assessment during the study	INCLUDE IN EVERYTHING
OTH07	Mishandling of secukinumab	INCLUDE IN EVERYTHING
OTH08	If subject of childbearing status=Able to bear children' at demography however urine pregnancy test is not performed or result is not available	INCLUDE IN EVERYTHING
OTH09	Physical examination is not conducted per protocol	INCLUDE IN EVERYTHING
OTH10	Central laboratory analyses not perfomred at a scheduled visit	INCLUDE IN EVERYTHING
OTH11	Patient included in the study and was on cholesterol or lipid lowering agent in treatment phase without stable dose for at least 12 weeks prior to baseline	INCLUDE IN EVERYTHING
OTH12	Patient included in the study and was on hypertensive drug in treatment phase without stable dose for atleast 12 weeks prior to baseline	INCLUDE IN EVERYTHING
OTH13	Patient included in the study and was on glucose lowering agent in treatment phase without stable dose for atleast 12 weeks prior to baseline	INCLUDE IN EVERYTHING
OTH15	Subject has missed study extension visit	INCLUDE IN EVERYTHING
OTH17	No study visit performed due to Covid-19 but study drug administered at home	INCLUDE IN EVERYTHING
OTH18	Missed Visit due to COVID-19	INCLUDE IN EVERYTHING

OTH19	Visit not done at study site due to COVID-19	INCLUDE IN EVERYTHING
OTH20	Assessment/Procedure changed due to COVID-19	INCLUDE IN EVERYTHING
OTH22	Study Discontinuation due to COVID-19	INCLUDE IN EVERYTHING

The protocol deviation list is a live document and can be modified during the conduct of the trial. All the protocol deviations effecting patient safety and/or data reliability & efficacy will be considered major in nature and will be documented and included in Quality tolerance limits. The final list and exclusion codes will be confirmed before the CDBL.

5.5 Visit windows and mapping of visits

Visit-windows will be used for safety & efficacy data that is summarized by visit; they are based on the study assessment schedule and comprise a set of days around the nominal visit day. For any assessment there will be a visit window to cover the complete range of days within the study. The analysis visit will be used for listing of visit and period. If a visit falls after the last visit window it is not assigned an analysis visit and will be listed under label "After Week 56"

Table 5-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-88
Week 16	16	113	Day 89-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183
Week 28	28	197	Day 184-211
Week 36 (E1)	36	253	Day 212-295
Week 44 (E2)	44	309	Day 296-379
Week 56 (E3)	56	393	Day 380-435

5.5.1 Multiple assessments within visit-windows

When there are multiple assessments in a particular visit-window, the following rules are applied to select one value "representing" the patient in summary statistics in a visit-window. The baseline value is represented by the last observation prior to the first dose unless otherwise specified.

For baseline assessment definition see Section 2.1.1.2.

For post-baseline visit-windows the following applies (unless otherwise specified):

- for quantitative variables, the closest to the actual visit is chosen (if two assessments have the same distance, than the earlier one will be chosen);
- for qualitative variables, the worst record is selected. It is noted that in the analyses performed, worst case is always well defined.
- in case qualitative variables are based on quantitative variables, e.g. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

6 Reference

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NOVARTIS

Clinical Development

CAIN457A/METABOLYX

CAIN457ADE08

A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4-weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque-type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period

Biomarker Sub-study Statistical Analysis Plan (SAP)

Author: [redacted]

Document type: SAP Documentation (Biomarker sub-study)

Document status: Amendment 1.0

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
11-May-2022	Prior to Final DB lock	Creation of final version	N/A - First version	NA
01-Jun-2022	Prior to Final DB lock	Creation of Amendment version 1.0	Additional analyses for separate fasting and fed conditions was removed from SAP, analyses for free fatty acid serum profile updated, Overlapping visit window period added.	Section 2.5.1, 2.5.2, 4 & 5.2

Table of contents

List of abbreviations

AE	Adverse Event
BAS	Biomarker Analysis Set
CRF	Case Report Form
CSR	Clinical Study Report
DMS	Document Management System
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model for Repeated Measures
NA	Not Applicable
RAP	Reporting & Analysis Process
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

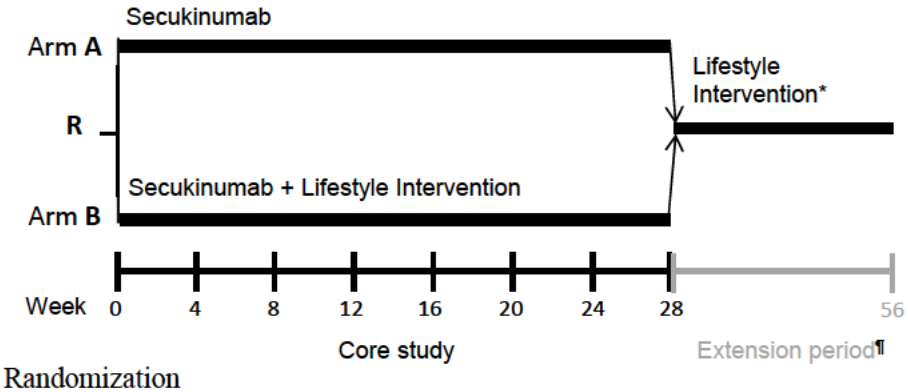
1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis for biomarker sub-study as planned in section 9.6 in the clinical study protocol version 00 for the clinical trial CAIN457ADE08 (METABOLYX). Additional analyses, specifications or deviations from the study protocol planned before database lock will also be discussed in this SAP.

1.1 Study design

This study is designed as a randomized, open-label, parallel-group, active comparator-controlled trial with two treatment arms. The design is shown in Figure 1-1.

Figure 1-1 Study Design



R: Randomization

* During the extension period the lifestyle intervention can be continued by patients who have been in arm B during the core study or it can be started by patients who have been in arm A. Participation in the lifestyle intervention during the extension period is **not** mandatory.

¶Participation in the extension period itself is mandatory. Psoriasis treatment during the extension period can be chosen freely by the Investigator. No study drug is supplied during the extension period.

Core study: After providing informed consent patients will be screened for eligibility for a period of 1-4 weeks prior to inclusion into the study. If eligible, patients will then be randomized to one of the two treatment arms, which are the following:

- **Arm A**: Patients in arm A receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28, where they complete the core study. The last Secukinumab injection is performed at week 24.
- **Arm B**: Patients in arm B receive a regular induction followed by 4-weekly maintenance treatment with Secukinumab 300 mg s.c. until week 28. The last Secukinumab injection is performed at week 24. **In addition to Secukinumab treatment patients in arm B participate in a lifestyle intervention program**.

A biomarker sub-study will be performed during the core study to explore the effect of secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to secukinumab alone on biomarkers including but not limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis/steatosis, heart failure, as well as to inflammatory processes in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with Secukinumab alone). At baseline (week 0), week 16 and week 28, the following markers will be assessed using **fasting blood samples**: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, and NT-proBNP.

The markers will be assessed centrally.

Clinically significant abnormal laboratory values for the following parameters of the biomarker sub-study will also be assessed (only for patients participating in the biomarker sub-study): adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, NT-proBNP.

1.2 Study objectives, endpoints and estimands

The exploratory biomarker sub-study objective and endpoints are described in Table 1-1.

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
To explore the effect of Secukinumab (300 mg, 4-weekly s.c.) combined with lifestyle intervention in comparison to Secukinumab alone on biomarkers including but not limited to those linked to lipid, glucose, muscle and bone metabolism, liver fibrosis/steatosis, heart injury, as well as to inflammatory processes in a subgroup of 100 patients (50 treated with secukinumab and lifestyle intervention and 50 treated with secukinumab alone)	At baseline (week 0), week 16 and week 28 the following markers will be assessed: Free fatty acid serum profile, sThy-1, adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, IL-1 beta, IL-1Ra, IL-18, IL-18bp, P1NP, CTX, RANKL, OPG, sclerostin, NT-proBNP, CD154, and a 30-panel multiplex inflammatory cytokine and chemokines panel

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

All statistical analysis will be performed by Novartis Business Services CONEXTS (NBS CONEXTS). Data will be analyzed by statistical software SAS version 9.4 according to the data analysis section 9.6 of the study protocol.

2.1.1 General definitions

Summary statistics for continuous variables will include N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, standard deviation (SD), median, minimum & maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed.

If not otherwise specified, p-values will be presented as two-sided p-values along with the two-sided confidence interval.

Unless otherwise stated, the level of significance will be set to 5% (two-sided).

Change from baseline and percentage change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated wherever applicable as:

Change from baseline = post-baseline value – baseline value.

Percentage change from baseline = ((Change from baseline value)/ (baseline value))*100

2.1.1.1 Study Treatment and Study Day

The day of randomization visit where the patients were allocated to their respective treatment arm i.e. Arm A or Arm B, respectively is defined as Day 1. All study days will be labelled relative to Day 1. Day 0 will not be used, the day before Day 1 is Day -1.

For events occurring on or after Day 1,

Study day = [Date of event]-[Date of first dose] + 1

For events occurring prior to Day 1,

Study day = [Date of event]-[Date of first dose]

2.1.1.2 Screening, baseline and post-baseline definitions

Screening period refers to the period starting from signing the informed consent until randomization or screening failure. Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment.

For efficacy analyses, baseline is the last available pre-dose assessment obtained at Visit 2. If the measurements at Visit 2 are missing, the measurements obtained at Visit 1 will be considered as the baseline. All assessments obtained after Visit 2 are considered as post-baseline.

For safety analyses, baseline is the last assessment obtained before the first dose of study treatment (i.e. secukinumab) at Visit 2. If the measurements at Visit 2 are missing, the measurement at Visit 1 will be considered as the baseline. All assessments obtained after the first dose of study treatment (i.e. secukinumab) are considered as post-baseline.

2.2 Analysis sets

The following analysis sets will be used for the data analysis.

Safety Set (SAF): The SAF will consist of all patients who received at least one dose of study treatment i.e. secukinumab. Patients will be analyzed according to the treatment they received, i.e. secukinumab alone or secukinumab with life-style intervention.

Biomarker Analysis Set (BAS): The BAS will consist of all patients in the Safety set (SAF), who have been enrolled in the biomarker sub-study & had at least one evaluable biomarker value.

All the statistical analyses for biomarker sub-study will be performed on the BAS dataset.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of patients enrolled, completed or discontinued from the biomarker sub-study, including reasons for discontinuation will be presented by treatment group for all patients in the BAS dataset.

Descriptive statistics for the background and demographic data will be provided for the BAS dataset. Continuous variables will be summarized using N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, median, standard deviation, minimum and maximum.

Frequency counts and percentages will be presented for categorical variables for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed. Two-sided 95% confidence intervals will be evaluated and reported for frequency percentages using Clopper-Pearson / Exact method.

2.3.2 Demographics and other baseline characteristics

The following data will be summarized for BAS dataset:

- age (in years, and year categories ≤ 65, > 65)
- gender (male/female)
- child bearing status (able to bear children/post-menopausal/sterile - of child bearing age)
- race (Asian/Caucasian/Black or African American/Unknown/Other)
- source of subject referral
- smoking status (never/current/former)
- average pack year (former/current/overall)
- height (cm)
- weight (kg)
- body mass index (BMI) = weight (kg) / (height (meters))^2
- waist circumference (cm)
- hip circumference (cm)
- waist to hip ratio = waist circumference (cm)/ hip circumference (cm)
- sitting pulse (bpm)
- systolic and diastolic blood pressure (mmHg)

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The number and percentage (%) of patients receiving injections will be summarized categorically (one fewer than all, two fewer than all etc.) for the core study using the BAS set by treatment groups and overall. The duration of exposure (days) to secukinumab study treatment will be presented similarly.

Duration of exposure is calculated as ((last known date of study medication (as per the DAR CRF) – start date of medication) + 1) / 7 (in weeks)

The duration of exposure will be reported in weeks.

Start date and last known date of study medication will be as per the drug accountability record eCRF page.

2.4.2 Prior, concomitant and post therapies

Not applicable.

2.4.3 Study compliance

2.4.3.1 Secukinumab

Compliance as percentage of injections administered will be calculated as the number of injections applied (based on documented study drug administrations and syringe counts as given in the dosage administration record eCRF page) divided by the number of injections scheduled per protocol. For dropouts/discontinuations, the denominator will be adjusted to number of injections scheduled per protocol until discontinuation.

Compliance is given by the formula:

Compliance (%) = 100*(total no of injections administered) / (no. of injections prescribed until discontinuation)

In the core study, two pre-filled syringes containing 150 mg secukinumab will be provided as open label medication at weeks 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 (last injection is at week 24).

Compliance percentage will be summarized for the BAS dataset (displaying totals) by treatment group and also by categories (< 80% and ≥ 80% to 100%).

2.4.3.2 Lifestyle intervention

Compliance as percentage of lifestyle intervention visits participated in will be calculated as the number of intervention visits attended (based on documented participation counts as given in the lifestyle intervention record eCRF page) divided by the number of lifestyle intervention visits scheduled per protocol until discontinuation. For dropouts/discontinuations, the denominator will be adjusted to number of intervention visits participated scheduled per protocol until discontinuation.

Compliance is given by the formula:

Compliance (%) = 100*(total no of lifestyle intervention visits participated) / (no. of lifestyle intervention visits scheduled)

In the core study, lifestyle intervention visits are scheduled at weeks 0, 1, 2, 3, 4, 8, 16 and 24.

Compliance percentage will be summarized for the BAS dataset (displaying totals) by treatment group and also by categories (< 80% and ≥ 80% to 100%).

2.5 Analysis supporting sub-study objective(s)

2.5.1 Primary endpoint(s)

At baseline (week 0), week 16 and week 28 the following markers will be assessed using fasting blood samples:

- Free fatty acid serum profile
- sThy-1
- Adiponectin
- Leptin
- Insulin
- HOMA-IR
- Proinsulin
- IL-6
- TNF-alpha
- M30 assay
- IL-1 beta
- IL-1Ra
- IL-18
- IL-18bp
- P1NP
- CTX
- RANKL
- OPG
- Sclerostin
- NT-proBNP

Free fatty acid serum profile is comprised of total 11 molecules i.e., Free fatty acid, Eicosatrienoic acid, Heptadecanoic acid, Linoleic acid, Linolenic acid, Oleic acid, Palmitic acid, Palmitoleic acid, Pentadecanoic acid, Stearic acid & Tetradecanoic acid. All the molecules will be analyzed separately for Free fatty acid serum profile.

2.5.2 Statistical hypothesis, model, and method of analysis

There will be no formal hypothesis testing in the biomarker sub-study.

All the biomarkers at weeks 0, 16, and 28 will be analyzed analogous to the sub-study endpoint. Absolute biomarker scores will be analyzed using a mixed model for repeated measures (MMRM), with factors treatment, center, visit, visit*treatment interaction and covariate baseline respective biomarker value. The raw as well as the adjusted least square means and

their differences between treatment groups will be calculated for each visit together with their corresponding 95% confidence intervals and p-values.

2.5.3 Handling of missing values/censoring/discontinuations

For all continuous variables, all available measurements will be included in the Mixed Model for Repeated Measures (MMRM).

2.6 Additional analysis

In order to explore the additional effect of lifestyle intervention on biomarker sub-study end-points, an additional analysis will be performed for all the study biomarkers at V9 (Week 16) & V12 (Week 28) for both treatment arms, separately based on three below mentioned subgroups:

- Patients with weight loss < 5%
- Patients with weight loss ≥ 5% - < 10%
- Patients with weight loss ≥ 10%

For all the above mentioned sub-groups, the no. of patients falling in each sub-group will be descriptively summarized using frequency, percentages and exact 95% Clopper-Pearson CI at V9 (Week 16) and V12 (Week 28) for both treatment arms, separately using BAS. Change in weight loss will be compared from the baseline weight.

All the patient's biomarkers value will be summarized descriptively using N, n, mean, median, standard deviation (SD), min and max for all the three subgroups using BAS. Absolute biomarker values will be analyzed using a MMRM with factors treatment, center, visit, visit*treatment interaction and covariate baseline biomarker value. The raw- as well as the adjusted (LS-) means and their differences between treatment groups will be calculated for each visit together with their corresponding 95% confidence intervals and p-values, for all the three sub-groups separately. Also, similar MMRM model will be used for all the biomarkers listed in section 2.5.1, for all the three sub-groups, separately.

All the above- mentioned analyses for all study biomarkers will be performed separately for both treatment groups for below mentioned comparisons:

a. Patients with weight loss ≥ 5% - < 10% vs. Patients with weight loss < 5%
b. Patients with weight loss ≥ 10% vs. Patients with weight loss < 5%
c. Patients with weight loss ≥ 5% - < 10% vs. Patients with weight loss ≥ 10%

2.6.1 Laboratory data

Clinically significant abnormal laboratory values will also be assessed for the following parameters of the biomarker sub-study (only for patients participating in the biomarker sub-study): Adiponectin, leptin, insulin, HOMA-IR, proinsulin, IL-6, TNF-alpha, M30 assay, NT-proBNP.

3 Sample size calculation

There is no formal sample size computation for the sub-study.

4 Change to protocol specified analyses

i. Creation of BAS

ii. Reporting of patient disposition, demographics and baseline characteristics as defined in section 2.3

iii. Reporting of study treatment compliance and study compliance as mentioned in section 2.4

iv. Additional analysis proposed for stratification of the analysis for all study biomarkers by the groups “patients achieving weight loss <5%”, “patients achieving weight loss ≥5% - <10%” and “patients achieving weight loss ≥10%” in each treatment arm.

5 Appendix

5.1 Statistical models

MMRM Model

Absolute biomarkers value will be analyzed using a Mixed Model for Repeated Measurements (MMRM) with factors treatment, center, visit, visit*treatment interaction and covariate baseline biomarker value.

```
proc mixed data = BAS covtest;
class subjid TRT01P siteid avisitn;
model CHG_B = base TRT01P siteid avisitn  avisitn*TRT01P/ ddfm=KR
residual;
repeated avisitn  / type=un subject=subjid rcorr;
estimate "Trt diff at Week 28" Trt 1 -1 TRT01P*avisitn 1 -1/cl;
lsmeans Trt*VisitWk / cl;
run;
```

Where,

BAS = dataset; TRT01P = Treatment arms (A & B); CHG_B = Change from Baseline

5.2 Visit windows and mapping of visits

Visit-windows will be used for biomarker sub-study data that is summarized by visit; they are based on the study assessment schedule and comprise a set of days around the nominal visit day. For any assessment there will be a visit window to cover the complete range of days within the study. So, the overlapping visit window period will be used for the analyses, as mentioned below in Table 5-1.

Table 5-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	0	1	-28 days to Day 1
Week 16	16	113	Day 99-127
Week 28	28	197	Day 183-225

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Clinical Development

CAIN457A/METABOLYX

CAIN457ADE08

A randomized, multicenter 28 week study to compare the efficacy and safety of combining Cosentyx (Secukinumab) (4 weekly, 300 mg s.c.) with a lifestyle intervention to Cosentyx therapy alone in adult patients with moderate to severe plaque type psoriasis and concomitant metabolic syndrome, followed by a 28 week extension period

Extension Period Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Addendum 1.0
Release date:	19-Sep-2022
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Template Version 4.0, Effective from 23-Apr-2021

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
27-Jul-2022	Prior to DB lock	Creation of final version	N/A - First version	NA
19-Sep-2022	After Final DB lock	Creation of Addendum version 1.0	Text modified in section 2.6.1	2.6.1

Table of contents

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
DLQI	Dermatology Life quality index
FAS	Full Analysis Set
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HRQoL	Health-related quality of life
IA	Interim Analyses
LDL	Low-density lipoprotein
LLN	Lower Limit of Normal
LOQ	Limit of Quantification
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
ULN	Upper Limit of Normal
WHO	World Health Organization

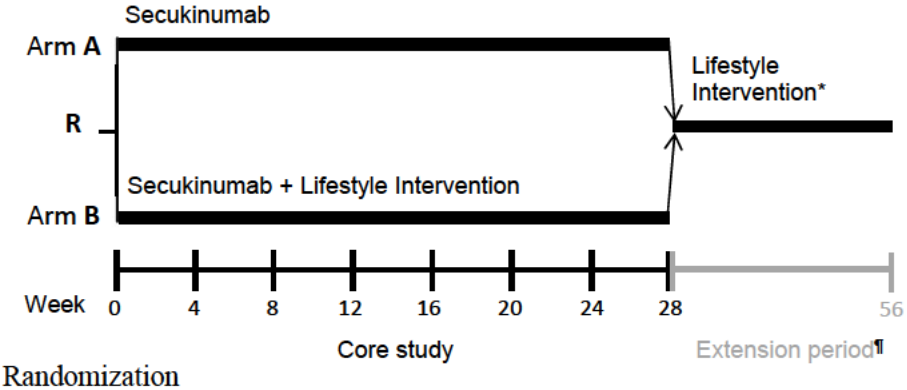
1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis for extension period as planned in section 9.7 in the clinical study protocol version 02 for the clinical trial CAIN457ADE08 (METABOLYX). Additional analyses, specifications or deviations from the study protocol planned before database lock will also be discussed in this SAP.

1.1 Study design

This study is a randomized, open-label, parallel-group, active comparator-controlled trial with two treatment arms. The design is shown in Figure 1-1.

Figure 1-1 Study Design



R: Randomization

* During the extension period the lifestyle intervention can be continued by patients who have been in arm B during the core study, or it can be started by patients who have been in arm A. Participation in the lifestyle intervention during the extension period is **not** mandatory.

¶Participation in the extension period itself is mandatory. Psoriasis treatment during the extension period can be chosen freely by the Investigator. No study drug is supplied during the extension period.

Extension period: After 28 weeks the study continues with an extension period, during which lifestyle intervention is offered to all patients, irrespective of their prior treatment arm. This means that patients of arm B, who are willing to, can continue their previously started lifestyle intervention program and patients of arm A, who are willing to, can start the lifestyle intervention program at the beginning of the extension period. **All patients, irrespective of their decision whether to start/ continue lifestyle intervention or not, have to participate in the extension period and visit their dermatologic study center for scheduled visits**. The extension period ends at week 56, where all patients complete the study. There will be no study

drug supply during the extension period. The treating physician can choose psoriasis therapy freely according to his/her discretion.

1.2 Study objectives and endpoints

2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

2.1 Data analysis general information

All statistical analysis will be performed by Novartis Business Services CONEXTS (NBS CONEXTS). Data will be analyzed by statistical software SAS version 9.4 according to the data analysis section 9.6 of the study protocol.

2.1.1 General definitions

Summary statistics for continuous variables will include N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, standard deviation (SD), median, minimum & maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed.

Unless otherwise stated, the level of significance will be set to 5% (two-sided).

2.1.1.1 Study Treatment and Study Day

The day when the patients complete core phase (Week 28) and enter extension period is defined as study Day 1 for Extension phase.

Study day=[Date of event]-[Date of first extension phase assessment] + 1

2.2 Analysis sets

The following analysis sets will be used for the data analysis.

Safety Set (SAF): The SAF will consist of all patients who received at least 1 dose of study treatment.

Full Analysis Set (FAS): The FAS will consist of all patients who completed the Core phase of the study and either discontinued or entered the extension period.

2.3 Patient disposition, demographics, and other characteristics

2.3.1 Patient disposition

The number and percentage of patients entering the extension period, completed or discontinued the study during extension period, including reasons for discontinuation will be presented by treatment group for all patients.

Descriptive statistics for the background and demographic data will be provided for the patients completed the core study and entering the extension period. Continuous variables will be

summarized using N (the number of subjects in the analysis set), n (the number of subjects with available/imputed value), mean, median, SD, minimum and maximum.

Frequency counts and percentages will be presented for categorical variables for non-missing data. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator. If a count of zero is obtained, the zero count and percentage will still be displayed. Two-sided 95% confidence intervals, if required, will be evaluated and reported for frequency percentages using the Clopper-Pearson Exact method.

2.3.2 Demographics and other characteristics

The following data will be summarized for FAS:

- age (in years, and year categories ≤ 65, > 65)
- gender (male/female)
- childbearing status (able to bear children/post-menopausal/sterile - of childbearing age)
- race (Asian/Caucasian/Black or African American/Unknown/Other)
- smoking status (never/current/former)
- average pack year (former/current/overall)
- height (cm)*
- weight (kg, and weight categories < 90, >=90)
- body mass index (BMI) = weight (kg) / (height (meters))^2
- waist circumference (cm)
- hip circumference (cm)
- waist to hip ratio = waist circumference (cm)/ hip circumference (cm)
- sitting pulse (bpm)
- systolic and diastolic blood pressure (mmHg)

*Height will be captured from the baseline vitals of the core study

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.2 Study Compliance

2.4.2.1 Lifestyle intervention

Compliance as percentage of lifestyle intervention visits participated in will be calculated as the number of intervention visits attended (based on documented participation counts as given in the lifestyle intervention record eCRF page) divided by the number of lifestyle intervention visits scheduled per protocol until discontinuation. For dropouts/discontinuations, the

denominator will be adjusted to number of intervention visits participated scheduled per protocol until discontinuation.

Compliance is given by the formula:

Compliance (%) = 100*(total no of lifestyle intervention visits participated) / (no. of lifestyle intervention visits scheduled)

In the extension period, lifestyle intervention visits are scheduled at weeks 36, 44, and 56.

Compliance percentage will be summarized for the FAS (displaying totals) by categories (< 80% and ≥ 80% to 100%).

2.4.3 Concomitant and post therapies

Concomitant medications along with non-drug therapies will be summarized using the FAS.

Any medication given at least once between the day of entering the extension phase and the last day of the extension visit will be a concomitant medication, including those which were started before commencing extension period and continued into the extension period.

Medications will be presented in order of frequency, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Preferred terms will be sorted by decreasing proportion and alphabetical order.

Tables will also show the overall number and percentage of subjects receiving at least one treatment in a particular ATC code.

2.6 Safety analyses

Safety analyses related to adverse event reporting will be based on the SAF. All the adverse from baseline till end of study (i.e. Week 56) will be reported cumulatively.

All Safety analyses for Extension period will be performed separately on the FAS.

2.6.1 Adverse events (AEs)

Treatment-emergent adverse events (events started after the administration of first dose of secukinumab in the Core phase or events present prior to the initiation of Core phase but increased in severity) will be summarized by preferred term. Additionally, AE(s) reported up to 84 days post Week 24 (i.e., till Week 36) will be considered as TEAEs.

All the AEs reported Week 36 onwards will be listed & summarized by preferred term up to last study assessment i.e., Week 56.

If a patient reports more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reports more than one AE within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable. Furthermore, a listing of all AEs, including SAE, will be provided. SAEs will be summarized.

In the extension period, the treating physician is free to choose suitable psoriasis therapy for each patient. Summaries will be presented for AEs by severity and for chosen therapy (marketed secukinumab, Novartis or Non-Novartis products) related AEs.

Separate summaries will be provided for death, SAE, other significant AEs leading to discontinuation of study grouped by therapy chosen by treating physician.

2.6.2 Deaths

Deaths occurring after entering the extension period will be listed and summarized separately, based on the FAS.

2.6.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry, and urinalysis) separately, for extension period, based on the FAS. Data for hematology, clinical chemistry, and urinalysis will be listed separately. All the laboratory parameters and markers with values below Limit of quantification (LOQ) will be reported as LOQ/2. Descriptive summary statistics for each study visit will be presented.

These descriptive summaries will be presented by laboratory test group, laboratory test. An additional summary table will be reported for the patients chosen for being administered secukinumab by the physician.

The below-mentioned laboratory parameters will be descriptively summarized. Frequencies and percentages will be presented for patients with clinically notable laboratory values, for the below-mentioned selected lab parameters:

Clinically notable laboratory values

Liver Function and Related Variables

- ALT (SGPT): > 3 x Upper Limit of Normal (ULN)
- AST (SGOT): > 3 x ULN
- Total bilirubin: > 1.5 x ULN
- Alkaline phosphatase: > 2 x ULN

Renal Function and Electrolyte Variables

- Creatinine (serum): > 1.5 x ULN

Hematology Variables

- Hemoglobin: ≥ 20 g/dL decrease from week 36
- Platelet count: < Lower Limit of Normal (LLN)
- White blood cell count: < 0.8 x LLN
- Neutrophils: < 0.9 x LLN
- Eosinophils: > 1.1 x ULN
- Lymphocytes: > 1.1 x ULN

Clinically significant abnormal laboratory values will also be summarized based on the FAS.

2.6.4 Other safety data

2.6.4.1 ECG and cardiac imaging data

Not applicable.

2.6.4.2 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from Week 36 for each visit of the extension period will be performed based on FAS. These descriptive summaries will be presented by vital sign and treatment group. Change from Week 36 will only be summarized for patients with both Week 36 and post-Week 36 values. Vital signs included are: weight (kg), BMI = weight (kg) / (height at visit 1 (meters))^2, waist circumference (cm), hip circumference (cm), waist to hip ratio = waist circumference (cm)/ hip circumference (cm), sitting pulse (bpm), systolic and diastolic blood pressure (mmHg).

2.7 Patient-reported outcomes

Descriptive statistics will be provided for all the patient related outcomes (PRO) mentioned in Section 5.3, using FAS.

2.8 Interim analysis

Not applicable.

3 Sample size calculation

No formal calculation is performed for the extension period. All the patients completing the core study will be moved to the extension period.

4 Change to protocol specified analyses

1. Full analysis set (FAS) has been redefined as per the Extension phase analyses requirements.
2. Additional safety analyses for Extension period have been included in the analyses.
3. Additional descriptive analysis added for PROs Self-assessed pain, itching, scaling and WHO-5 scale.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 AE end date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e., including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, 31DECYYYY, date of death.
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, last day of the month, date of death.
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date, use AE start date as AE end date.

5.1.1.2 AE start date

AEs with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment within this study.

Partial AE start dates are imputed with reference to the first administration of study treatment within this study as outlined in the table below.

The date value is split into day, month, year sections and referenced in the imputation table as outlined below.

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start	(C) = 15MONYYYY Before Treatment Start

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Treatment Start	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start	(A) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates AE start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates AE start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, Treatment Start +1)
(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

Before imputing the AE start date, find the AE start reference date.

- If the AE end date is complete and the (imputed) AE end date < Treatment Start Date then AE start reference date = min (study informed consent date, earliest visit date).
- Else AE start reference date = Treatment Start Date

To impute AE start date:

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the study treatment start date year value, the AE started before study treatment. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the study treatment start date year value, the AE started after study treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the study treatment start date month or greater than the study treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication end date

To impute concomitant end date:

1. If the concomitant end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the concomitant end year value is missing or ongoing, the imputed concomitant end date is set to NULL.
2. Else, if the concomitant end date month is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, 31DECYYYY, date of death.
3. If the concomitant end date day is missing, the imputed end date should be set to the earliest of the following: study treatment follow-up period date, last day of the month, date of death.

If the imputed concomitant end date is less than the existing concomitant start date, use the concomitant start date as the imputed concomitant end date.

5.1.2.2 Concomitant medication start date

Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the first administration of study treatment within this study in accordance with the rules outlined below.

	Day	Month	Year
Partial Concomitant medication (CMD) Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY<TRTM	(D) = 01JULYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start	(A) = 15MONYYYY Before Treatment Start
YYYY=TRTY	(C) Uncertain	(A) = 15MONYYYY Before Treatment Start	(C) Uncertain	(B) = 01MONYYYY After Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start	(B) = 01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment start	Partial date indicates CMD start date prior to Treatment Start Date in this study
After Treatment start	Partial date indicates CMD start date after Treatment Start Date in this study
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date in this study
Imputation calculation	
NC/Blank Uncertain	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, Treatment Start Date +1)
(C) Uncertain	IF CMDTYP IN (1, 3) THEN Treatment Start Date -1

Relationship	
	ELSE IF CMDTYP IN (. 2) THEN Treatment Start Date +1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

To compute concomitant start date:

1. If the concomitant start date year value is missing, the imputed concomitant start date is set to one day prior to study treatment start date.
2. If the concomitant start date year value is less than the study treatment start date year value, the concomitant medication started before study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the mid-year point (01JULYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
3. If the concomitant start date year value is greater than the study treatment start date year value, the concomitant started after study treatment. Therefore:
   a. If the concomitant month is missing, the imputed concomitant start date is set to the year start point (01JANYYYY).
   b. Else if the concomitant month is not missing, the imputed concomitant start date is set to the month start point (01MONYYYY).
4. If the concomitant start date year value is equal to the study treatment start date year value:
   a. And the concomitant month is missing or the concomitant month is equal to the investigational treatment start date month, then the imputed concomitant start date is set to one day prior to investigational treatment start date.
   b. Else if the concomitant month is less than the investigational treatment start date month, the imputed concomitant start date is set to the mid-month point (15MONYYYY).
   c. Else if the concomitant month is greater than the investigational treatment start date month, the imputed concomitant start date is set to the month start point (01MONYYYY).

If complete (imputed) concomitant end date is available and the imputed concomitant start date is greater than the (imputed) concomitant end date, then imputed concomitant start date should be set to the (imputed) concomitant end date.

5.2 Statistical models

Not applicable.

5.3 Patient reported outcomes (PRO)

PROs will be assessed by the following validated instruments.

• Dermatology Life Quality Index (DLQI©)

• Self-assessed pain, itching, scaling

• WHO-5

Dermatology Life Quality Index (DLQI©)

The DLQI© is a 10-item general dermatology disability index designed to assess Health-related quality of life (HRQoL) in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan 1994; Basra et al 2008).

The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 33 different skin conditions and is available in 85 languages. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The recall period is the previous week, and the instrument takes 1 to 2 minutes to complete.

Each item has four response categories including 0 (not at all), 1 (a little), 2 (a lot), and 3 (very much). "Not relevant" is also a valid response and is scored as 0.

The DLQI© total score is the sum of the 10 questions. Scores range from 0 to 30, with higher scores indicating greater HRQoL impairment. Each subscale of the DLQI© may also be analyzed separately.

Meaning of DLQI Scores

- 0-1= no effect at all on subject's life
- 2-5= small effect on subject's life
- 6-10= moderate effect on subject's life
- 11-20= very large effect on subject's life
- 21-30= extremely large effect on subject's life

DLQI response 0/1 variable will be calculated based on the DLQI total score as follows:

- 0 (Responders) – If DLQI total score is either 0 or 1
- 1 (Non-Responders) – If DLQI total score is > 1

Subject's self-assessed pain, itching and scaling

A self-administered, 11-point numeric rating scale (NRS, 0-10) will be used to evaluate the subject's assessment of their current pain, itching and scaling. Respondents will answer the following questions for the assessment of

- **Pain:** Overall, how severe was your psoriasis-related pain over the past 24 hours
- **Itching:** Overall, how severe was your psoriasis-related itch over the past 24 hours
- **Scaling:** Overall, how severe was your psoriasis-related scaling over the past 24 hours

Subjects have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e. no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (i.e. pain, itching or scaling as bad as it could be). The number that the patient selects represents his or her intensity score.

WHO-5

The 5-item World Health Organization Well-Being Index (WHO-5) is a validated, short questionnaire consisting of 5 simple questions, assessing subjective psychological well-being of the respondents. It is among the most widely used questionnaires for the assessment of psychological well-being and has been successfully applied across a wide range of study fields.

The measure is self-administered and takes approximately one minute to complete. The recall period is the previous two weeks. Each item has 6 response categories, ranging from 5 ("the whole time") to 0 ("at no time point"). The WHO-5 total score is the sum of the 5 questions. Each subscale of the WHO-5 may also be analyzed separately.

6 Visit windows and mapping of visits

Visit windows will be used for safety & efficacy data that is summarized by visit; they are based on the study assessment schedule and comprise a set of days around the nominal visit day. For any assessment there will be a visit window to cover the complete range of days within the study. So, the overlapping visit window period will be used for the analyses, as mentioned below in Table 5-1. If a visit falls after the last visit window it is not assigned an analysis visit and will be listed under label "After Week 56".

Table 6-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Week 36 (E1)	36	253	Day 212-295
Week 44 (E2)	44	309	Day 296-379
Week 56 (E3)	56	393	Day 380-435

7 References

Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY (2008) The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol; 159: 997-1035.

Finlay AY and Khan GK (1994) Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. Clin Exp Dermatol; 19: 210-216.