NOVARTIS

Clinical Development

AIN457A/Secukinumab®

CAIN457AUS07

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to explore changes in cutaneous adipose tissue and modulation of skin inflammation after 12 weeks of treatment with secukinumab, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult patients with moderate to severe plaque psoriasis (ObePso-S)

Statistical Analysis Plan (SAP)

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20-Nov-17	Prior to DBL	Amendment	[redacted]	Section 2.12
09-May-19	Prior to DBL	Amendment	As discussed in RAP meeting	

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List of abbreviations

AE	Adverse event
BMI	Body Mass Index
(e)CRF	(electronic) Case Report/Record Form
CRO	Contract Research Organization
CS	Corticosteroids
CT	Computerized tomography
GGT	gamma glutamyl transpeptidatse
hs-CRP	high sensitivity C-reactive protein
HOMA-IR	Homeostatic model assessment-insulin resistance
[redacted]	[redacted]
i.v.	Intravenous
IRT	Interactive Response Technology
LS	Lesional
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
SAE	Serious Adverse Event
s.c.	Subcutaneous
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SOP	Standard Operating Procedure
TB	Tuberculosis
TNF	tumor necrosis factor

Introduction

This statistical analysis plan (SAP) describes the statistical methodologies which will be used in the phase IV clinical trial (CAIN457AUS07). This is an exploratory, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with moderate to severe plaque psoriasis patients.

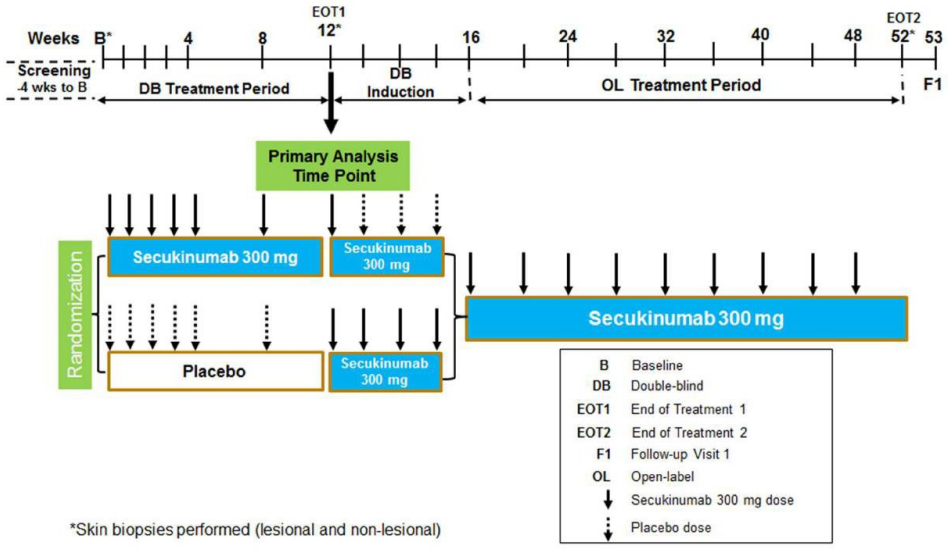
The purpose of this study is to explore changes in subcutaneous adipose tissue and skin inflammation in patients with moderate to severe plaque psoriasis treated with secukinumab 300mg compared to placebo at Week 12.

1.1 Study design

This study uses a randomized, double-blind, placebo-controlled, parallel-group, multicenter design. The study consists of five periods:

- Screening (from 1-4 weeks before randomization);
- Double-blind Treatment Period (Randomization to Week12 pre-dose);
- Double-blind Induction Period (Week 12 post dose to Week 15 dose);
- Open-label Treatment Period (Week 16 to Week 52); and
- Follow-up Period (1 week).

A schematic of the study design is presented below:



Approximately 75 moderate to severe plaque psoriasis patients (50 in secukinumab group and 25 in placebo group) from approximately 15 sites will be randomized at Visit 2/Baseline in a 2:1 ratio

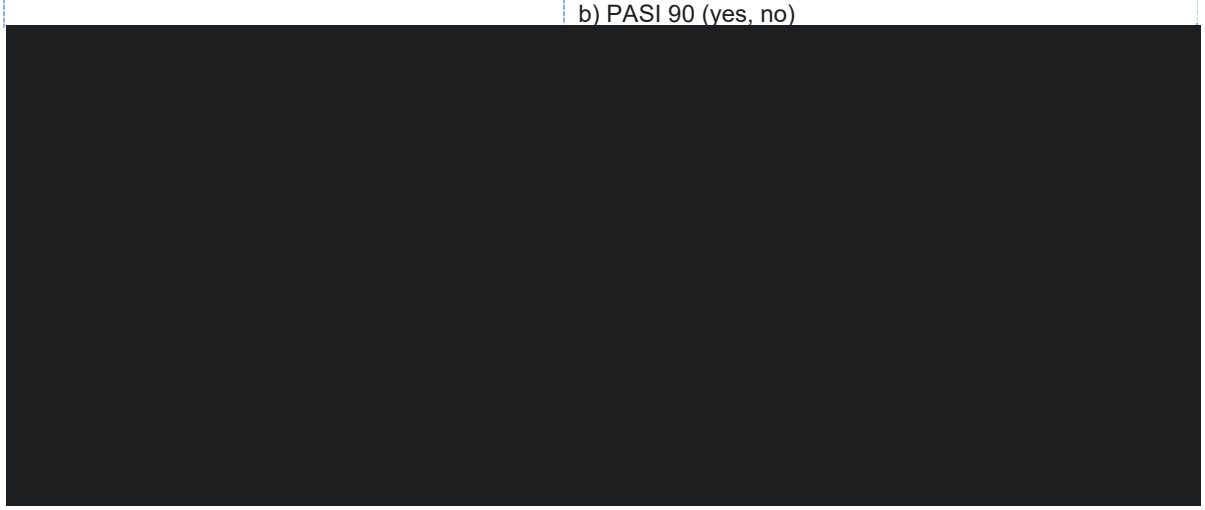
to receive secukinumab 300 mg or placebo, respectively. Randomization will be stratified by body weight collected at Visit 2 (<90 kg or ≥90 kg).

An interim analysis is planned after Week 12, which is the primary analysis time point for the study. Interim analysis will be performed after all patients have completed the Week 12 visit and the database is locked.

1.2 Study objectives and endpoints

Table 1.1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo	Response of psoriasis skin lesions to treatment as measured by: a) Response in skin histology/K16 expression to treatment (yes, no) b) PASI 90 (yes, no)
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To explore changes in biometric measurements from baseline to Week 12 in patients with moderate to severe plaque psoriasis treated with secukinumab compared to placebo	Vital signs (blood pressure, weight, waist circumference, BMI), clinical laboratory variables (glucose, insulin, hs-CRP, HOMA-IR, HbA1c)
To explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 52 in patients with moderate to severe plaque psoriasis treated with secukinumab	Response of psoriasis skin lesions to treatment as measured by: a) Response in skin histology/K16 expression to treatment (yes, no) b) PASI 90 (yes, no)



[redacted]

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the statistical analysis.

Data will be analyzed by the statistical software SAS, Version 9.4 according to Section 9 (Data Analysis) of the study protocol which will also be available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is given in the following sections and details are provided, as applicable, which will also be in Appendix 16.1.9 of the CSR.

Data up to Week 12 will be presented for the Week 12 interim analysis and all data will be presented for final analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of patients will be available for analysis.

Summary statistics for continuous variables will include n, mean, standard deviation, standard error of the mean, minimum, lower quartile, median, upper quartile, interquartile range, and maximum.

Summary statistics for discrete variables will be presented in contingency tables and will include frequencies and percentages.

Primary [redacted] efficacy variables will be summarized for lesional [redacted] samples.

2.1.1 General definitions

2.1.1.1 Study treatment

At Visit 2/Baseline, eligible patients will be randomized to one of the following two treatment groups in a ratio of 2:1:

Secukinumab group

Patients (or trained caregivers) will administer a dose of secukinumab 300 mg s.c. (two injections of the 150 mg PFS) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by dosing every four weeks, starting at Week 8 through Week 48. In order to maintain the blinding for the 12-week, placebo-controlled period, two injections of the placebo PFS will be administered at Weeks 13, 14, and 15 during the Double-blind Induction Period.

Placebo group

Patients (or trained caregivers) will administer a dose of placebo s.c. (two injections of the placebo PFS) once weekly for five weeks (at Baseline, Weeks 1, 2, 3, and 4), followed by a dose after four weeks at Week 8. Beginning at Visit 8/Week 12, all patients in the placebo group will be switched to treatment with secukinumab 300 mg s.c. Patients will receive a dose of secukinumab 300 mg s.c. (two injections of the 150 mg PFS) once weekly for five weeks (at Weeks 12, 13, 14, 15, and 16) followed by dosing every four weeks starting at Week 20 through Week 48.

Table 2-1 Overview of study treatment

Treatment group	DB Treatment Period *(Rand – Wk 12 pre-dose)*	DB Induction Period *(Wk 12 – Wk 15)*	OL Treatment Period *(Wk 16 – Wk 52)*
Secukinumab 300 mg	2x s.c. secukinumab 150 mg injection at BSL, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wk 12 2x s.c. PBO injection at Wks 13, 14 and 15	2x s.c. secukinumab 150 mg injection at four-week intervals from Wks 16 – 48
Placebo (PBO)	2x s.c. PBO injection at BSL, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wks 12, 13, 14, and 15	2x s.c. secukinumab 150 mg injection at four-week intervals from Wks 16 – 48

DB = Double-blind; OL = Open-label; PBO = placebo; BSL = Baseline; Wk = Week

2.1.1.2 Study day 1 and other study days

The day of first administration of the double blind randomized treatment will be considered as study day 1. All other study days will be labeled relative to study day 1. The day for a particular event on or after the study day 1 will be calculated as:

(date of event) - (date of first dose) + 1.

For example, study day 2, study day 3,…, will be one day, two days,…, after study day 1, respectively.

The day before study day 1 will be calculated as:

(date of event) - (date of first dose).

For example, study day -1, study day -2,…, will be one day, two days,…, before study day 1, respectively.

The descriptor “study day 0” will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis).

For efficacy analyses, baseline is the last assessment, i.e. the last non-missing observation, (including unscheduled visits) obtained before the randomization. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained on or before the first dose of study treatment (i.e. treatment start date). All assessments obtained after the first dose of study treatment are considered as post-baseline unless otherwise specified.

In general, a baseline value refers to the last measurement made prior to administration of the first dose of study treatment. However, LAB assessments if no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the CRF. The patient's exposure will be calculated considering the end of treatment period visit (e.g., treatment completion visit). If a patient discontinued early, then the last dose + 84 days or the last visit during the study whichever occurs earlier is considered.

Duration of exposure is defined in Section 2.4.1.

2.2 Analysis sets

The following analysis sets will be used for the statistical reporting and analyses:

Randomized Set (RAN): The Randomized Set includes all randomized patients.

Safety Set (SAF): The Safety Set includes all patients who received at least one dose of study medication. Patients will be included in the analysis according to treatment received.

Full Analysis Set (FAS): The Full Analysis Set comprises all patients to whom study medication has been assigned. Patients inappropriately randomized (e.g., IRT was called in error for randomization of a screen failed patient) will be excluded from this analysis set. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

2.2.1 Subgroup of interest

The primary efficacy variables and [redacted] efficacy variables will be evaluated using randomization weight strata: "body weight <90 kg", "body weight ≥90 kg".

2.3 Patient disposition, demographics and other baseline characteristics

The summaries will be shown separately for double-blind treatment period (before or at Week 12) and open-label treatment period (after Week 12):

In double-blind treatment period 1 for following treatment groups:

Secukinumab 300 mg, Placebo, Total

In open-label treatment period 2 for following treatment groups:

Secukinumab 300 mg, Placebo / Secukinumab 300 mg and Total

No summaries for entire treatment period will be provided

2.3.1 Patient disposition

The number of patients screened will be presented along with the reasons for screen failures for all patients as specified in the screening phase disposition eCRF.

The number and percentage of patients in the randomized set (RAN) who, completed study periods (double-blind treatment period and open-label treatment period) and who discontinued the study prematurely including the reason for discontinuation will be presented for each treatment group and all patients.

Patients withdrawing consent will be listed with reason for withdrawal.

The number and percentage of patients with protocol deviations will be tabulated by treatment groups and listed separately by treatment groups.

2.3.2 Demographics

The following common demographic variables will be summarized:

Continuous variables:

- Age (years) (which is derived from year of birth and the Informed Consent date)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m**2)

Body Mass Index (*BMI*) will be calculated using the following formula:

- BMI = (body weight in kilograms) / (height in meters)^2

Note: For BMI, height, and body weight, the last value prior to randomization is used. If there is no weight recorded prior to taking of study treatment, BMI will be missing.

Of note: patient's height will not be remapped according to the analysis visit window.

Categorical variables:

- Body weight category (<90 kg / ≥90 kg)
- Sex (male/female)
- Race (Caucasian/Black/Asian/Native American/Pacific Islander/Unknown/Other)

- Ethnicity (Hispanic or Latino/ Not Hispanic or Latino)
- Smoking status at baseline (Never/Current/Former)

2.3.3 Baseline disease characteristics

The following baseline disease characteristics and history of disease will be summarized for each treatment group and all patients in the Randomized Set and for Full Analysis Set.

- Baseline PASI score
- [redacted]
- Time since diagnosis of plaque psoriasis
- Psoriatic arthritis (yes, no)
- Time since diagnosis of psoriatic arthritis

The previous exposure to psoriasis treatments (biologic systemic psoriasis therapy, non-biologic systemic psoriasis therapy, topical therapy, phototherapy and photo-chemotherapy) along with body location with their duration of exposure and the reason for discontinuation will also be reported.

Unless otherwise specified, for all demographic and baseline disease characteristics, summary statistics will be presented for continuous variables for each treatment group and for all patients (total) in the Randomized Set and Full Analysis Set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients (total) in the Randomized Set and Full Analsysis Set.

In addition, all the above demographic and baseline disease characteristics variables will be summarized by body weight stratum (90 kg, ≥90 kg) in the Randomized Set and Full Analysis Set.

Time since diagnosis will be calculated using the following derivation:

Duration= (Screening (Visit 1) date - date of diagnosis) + 1

Relevant medical history/current medical conditions

Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary and they will be summarized by System Organ Class (SOC) and Preferred Term (PT) in treatment group.

Summaries for cardiovascular medical history will be summarized by categories and treatment group. Frequency and the percentage of the occurrence of each category will be presented. Ongoing cardiovascular disease will be flagged.

Alcohol and Smoking history will be summarized by treatment group.

Unless otherwise specified, analyses will be based on the Safety Set.

Smoking history

Smoking history collected at Visit 1 will be summarized descriptively in terms of estimated number of pack-years based on the approximate consumption per-year.

The patient's tobacco usage status (never, current, former) will be collected and frequency and percentage of different status will be presented by treatment.

Time since last date of tobacco use (for former category) will be summarized descriptively and its duration is calculated as follows:

Date of Visit 1 - Date of last use of tobacco + 1.

Alcohol use history

Alcohol use history will be summarized descriptively in terms of estimated number of alcoholic drinks consumed per day captured at Visit 1.

Time since last date of alcohol consumption will be summarized descriptively and calculated as follows:

Date of Visit 1 – Date of last alcohol consumption + 1.

Tuberculosis risk assessment

Determination of tuberculosis (TB) status should be assessed at Visit 1. TB status must be determined by medical history, signs, symptoms and TB testing (QuantiFERON-TB Gold assay).

If the QuantiFERON-TB Gold assay test is positive or indeterminate, a TB workup will be performed.

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

2.4.1 Study treatment / compliance

The analysis of study treatment and compliance data will be based on the safety set.

The number of secukinumab 1mL syringes, secukinumab placebo injections will be summarized by treatment group by means of contingency tables.

The duration in days will be summarized by treatment, descriptively and using frequencies and percentages for categories "any exposure", "≥1 week", "≥2 weeks", "≥3 weeks", "≥4 weeks", "≥8 weeks", "≥12 weeks", "≥16 weeks", "≥28 weeks", "≥40 weeks" and "≥52 weeks".

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit (including follow-up visits) whichever occurs earlier, i.e., for patients who discontinued or have their last visit earlier than 84 days, the end of study

treatment exposure will be the date of the last study visit in the follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min (last study visit (including follow-up if applicable) date, last dose date + 84) – first dose date + 1

Duration of exposure (years) = duration of exposure (days) / 365.25

The analyses of duration of exposure described above will be done for the treatment period up to Week 12 for the interim analysis, with the last category "≥12 weeks".

Compliance of treatment:

Compliance of treatment is defined as percentage of injections administered and 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.

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

Compliance to study treatment will be summarized descriptively and by categories:

<80%, and 80% - 100%, by treatment groups.

2.4.1.1 Visit windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 1-1. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments, and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. For example, if the Week 4 visit of a patient is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a patient may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Of note, patients are allowed to have gaps in visits.

Table 1-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 to 1 day
Week 4	4	29	Day 2-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-88
Week 16	16	113	Day 89-141
Week 24	24	169	Day 142-197
Week 32	32	225	Day 198-253
Week 40	40	281	Day 254-309
Week 48	48	337	Day 310-351
Week 52	52	365	Day >=352

For data which are not collected at every visit (for ex: [redacted], waist circumference etc.), visit windows will be combined from above Table 1-1. For example, if an assessment is at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 88 (combining Week 1 to Week 12 visit windows); Week 24 will extend from Day 89 to Day 197 (combining Week 13 to Week 24). If more than one assessment falls into the interval, the rules defined in following section below are applied.

Assessments from treatment period 2 will not be considered for treatment period 1, and treatment period 1 visits will not be mapped into treatment period 2.

For patients who prematurely discontinued, efficacy measurements taken in follow-up period will be remapped to treatment periods.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window (after Day376), it is not assigned an analysis visit and will be listed under label "After Week 53".

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.

- For baseline assessment:

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained before the randomization. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment. All assessments obtained after the first dose of study drug are considered as post-baseline unless otherwise specified.

- 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, then 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 (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
  - in case qualitative variables are based on quantitative variables, e.g., [redacted], the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-4 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement prior to first dose – note this may include measurements taken on the day of randomization (e.g., lab).
Post-baseline safety	Summary visit information (e.g., lab, ECG, vital etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the first one will be used. If two measurements are taken on the same day, then select the first one (using the time). If two measurements are taken on the same date/time, then use the first visit number (assuming this is the planned visit). If two measurements are taken on the same date/time/CRF visit, then use the average of two assessments
Post-baseline efficacy	All data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurement are taken on the same day then select the first one using eCRF visit number.
Post-baseline safety	Summary visit information	The (non-missing) measurement closest to the

Timing of measurement	Type of data	Rule
	(e.g., laboratory values, vital signs, etc.)	target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first eCRF visit number (assuming this is the planned visit).If two measurements are taken on the same date/time/eCRF visit number then take the average value of these two results.
Post-baseline safety and efficacy	Notable abnormalities (e.g., vital signs, PGIC) and CTCAE grading for laboratory values	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window

2.4.2 Prior, concomitant and post therapies

Prior and concomitant treatments will be summarized by treatment group for the Safety Set unless otherwise specified. Concomitant treatments will be displayed for the treatment period 1 and entire treatment period.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment.

Concomitant medications are defined as any medication administered at least once between the day of first dose and the last day of study visit, other than study medication, including those which were started pre-baseline and continued into the treatment period.

Any medication administered during the six months prior to study enrollment will be considered as prior and concomitant medication.

Medications will be identified and presented in alphabetical order, using Novartis drug and therapy dictionary (NovDTD) and by Anatomical Therapeutic Chemical (ATC) codes and grouped by anatomical main group (the first level of the ATC codes).

Prior and concomitant treatments will be summarized by treatment group using frequency count and percentages for the Safety Set, unless otherwise specified.

Table will also show the overall number and percentage of patients receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

In addition, medical procedures and significant non-drug therapies as coded in MedDRA will be summarized.

Treatment used, dose and date of administration will be listed. Duration of exposure will be presented by treatment if treatment is stopped during study period. Ongoing treatments will be flagged.

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Further rules will be given in Section 5.1.3.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary efficacy variables are the response of psoriasis skin lesions to treatment as measured by:

a) Response in skin histology/K16 expression to treatment (yes, no) (at Week 12)

b) PASI 90 (yes, no) (at Weeks 4, 8, and 12)

The primary analysis time point will be at Week 12.

2.5.1.1 Definition of PASI and related variables

The investigator or trained qualified designee will complete the PASI assessments. Whenever possible, the same evaluator should perform this assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 2-5.

A PASI score will be derived as indicated in Table 2-5. 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 help the assessment:

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 will be calculated using the formula:

$PASI = 0.1 (E_h + I_h + D_h)A_h + 0.2 (E_u + I_u + D_u)A_u + 0.3 (E_t + I_t + D_t)A_t + 0.4 (E_l + I_l + D_l)A_l$,

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 2-5).

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 investigator is responsible for collecting the components or scoring signs and total regional area for all visits. PASI and total BSA calculations will be done by investigator at screening and randomization only; The PASI scores after randomization will be calculated by Novartis and will be used in the analysis and for derivation of PASI response values (see below).

Table 2-5 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% 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.

The following definitions are possible efficacy evaluations that can be used in clinical trials in psoriasis:

- [redacted]
- [redacted]
- **PASI 90 response**: patients achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders

[redacted]

2.5.2 Statistical method of analysis

- Response of skin histology/K16 expression to treatment (yes, no) (at Week 12)

Difference between the two treatment groups –(secukinumab 300 mg versus placebo) with respect to percentage of patients who have a negative ("no") response to skin histology/keratin 16 to treatment at Week 12, will be presented along with 95% confidence interval. Confidence interval will be calculated using normal approximation to the binomial distribution.

- PASI 90 (yes, no) (at Weeks 4, 8, and 12)

Same method of analysis as described above will be used for PASI 90 response (yes, no) at Weeks 4, 8, and 12.

The primary analysis of the primary efficacy variables will be based on the Full Analysis Set.

2.5.3 Handling of missing values/censoring/discontinuations

For the primary efficacy variable K16 expression to the treatment at Week 12 (and other time points), a patient with a missing assessment will be considered as having a positive ("yes") response regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues). Patients who discontinue the trial for any reason will be considered as having a positive ("yes") response from the time they drop out through Week 52.

For the primary efficacy variable PASI90 response at Week 12 (and other time points), a patient with a missing assessment will be considered as a non-responder regardless to the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues). Patients who discontinuethe trial for any reason will be considered non-responders from the time they drop out through Week 52.

2.5.4 Supportive analyses

Sensitivity analyses will be performed as follows:

The two primary efficacy variables will be analyzed at each time point (as describe in section 2.5.1) with non-responder imputation using a logistic regression model with treatment and body weight (< 90 kg, ≥90kg) as explanatory variables (Stokes, Davis, and Koch, 2012). The odds ratio and 95% confidence intervals for odds ratios (secukinumab 300 mg versus placebo) based on the fitted model will be reported.

In addition, estimates of differences between the two proportions within each stratum will be calculated using treatment-by-stratum interaction in the above model, separately. The odds ratio and 95% confidence intervals for odds ratios will be reported to examine meaningful treatment difference by strata.

This logistic regression analysis will not be performed if the data is sparse (quasi-separated or completely separated).

The sensitivity analysis will be done based on the Full Analysis Set.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective

2.7.1 Secondary endpoints

The secondary efficacy objective (i.e., explore the modulation of subcutaneous adipose tissue and skin inflammation from baseline to Week 52) will be assessed using the same two primary efficacy variables, but measured at Week 52.

2.7.2 Statistical method of analysis

For the response of psoriasis skin lesions to the treatment, percentages of patients who have the “event” (as described in Sections 2.5.1 and 2.7.1) at Week 52 will be presented.

This secondary efficacy analysis will be done based on the Full Analysis Set.

2.7.3 Handling of missing values/censoring/discontinuations

See Section 2.5.3.

2.8 Safety analyses

All safety analyses will be based on the Safety Set. Only those scheduled visits which were pre-planned in the protocol will be reported in tables and figures for safety variables.

Treatment groups for evaluation of entire treatment

The summaries of evaluation will be reported for double-blind treatment period and entire treatment period, respectively.

The following groups will be used for double-blind treatment period :

- Secukinumab 300mg
- Placebo

The following groups will be used for entire treatment period:

- Secukinumab 300mg
- Placebo / Secukinumab 300 mg

2.8.1 Adverse events (AEs)

All treatment emergent adverse events starting on or after the first dose of study treatment and until the last dose of study treatment plus 7 days (30 days for serious adverse events [SAEs]) will be included in all summaries and listings.

The definition for “treatment emergent” is as below:

- events started after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term
- and started prior to the last dose plus 7 days (inclusive)

All adverse events will be coded using MedDRA dictionary and summarized by Primary system organ class (SOC) and preferred term (PT)using frequency and percentage.

Primary system organ classes will be sorted alphabetically and within each primary system organ class, the preferred terms will be sorted in descending order of frequency.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event.

Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE ‘severity’ is missing, this variable will be listed as missing and treated as missing in summaries. 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 system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

Any other information collected (e.g., severity or relatedness to study medication) will be listed, as appropriate.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT) will be presented in descending frequency according to its incidence in secukinumab group starting from the most common event. Here threshold value z is set to 2 (%) but it may be updated following review of the dry run outputs.

Serious Adverse Event (SAE)

Number and percentage of patients with serious adverse events, regardless of study drug relationship, will be presented by primary system organ class and preferred term. Primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency.

All SAEs will be listed.

If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

Separate summaries will be provided for deaths, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment or interruption.

Algorithms for date imputations will be provided in Section 5.1.2.

Adverse events and serious adverse events up to and including Week 12 visit will be included in the database for the analysis at the primary analysis time point (Week 12). All Adverse events and serious adverse events will be included in the final database analysis (Week 53).

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

Separate summaries and listings will be provided for deaths for each treatment period.

2.8.3 Laboratory data

The following laboratory variables will be analyzed:

- Hematology, which includes:

  hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count
- Clinical chemistry, which includes:

urea, creatinine, total bilirubin, alanine transaminase (ALT)/serum glutamic pyruvate transaminase (SGPT), aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidatse (GGT), and alkaline phosphatase

- High-sensitivity C-reactive protine (hs CRP)
- Hemoglobin A1c
- Fasting laboratory evaluations
    - Plasma glucose
    - Insulin
    - Lipids
- Viral serology
    - Hepatitis screening: Hepatitis B surface antigen (HBsAg); Hepatitis C virus antibody (HCVAb)
    - HIV screening: HIV 1/2

Descriptive summary statistics for the change from baseline to study visit will be presented by laboratory variable and weight stratum and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as: change from baseline = post-baseline value - baseline value.

The following laboratory variables will be analyzed with respect to the notable ranges:

Table 2-6 Criteria for notable abnormalities of hematology values

Variables	Notable abnormalities
Hemoglobin	≥ 2.0 g/dL decrease from baseline
Platelet count	< Lower Limit of Normal (LLN) White
blood cell	< 0.8 x LLN
Neutrophils	< 0.9 x LLN
Eosinophils	> 1.1 x ULN
Lymphocytes	> 1.1 x ULN

Table 2-7 Criteria for notable abnormalities of clinical chemistry values

Variables	Notable abnormalities
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

For each variable, the maximum change (maximum decrease and maximum increase) from baseline, within treatment period, will be summarized analogously.

In addition, shift tables will be provided for all variables to compare a patient's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the reference laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within a treatment phase (either initial or entire) will be presented as well (including category "high and low"). These summaries will be presented by laboratory variable and treatment group.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Descriptive summary statistics for change from baseline for each post-baseline visit will be presented by vital signs, weight stratum, and treatment groups, as appropriate. Change from baseline will be calculated only for the patients with both baseline and post-baseline values and will be calculated as: change from baseline = post-baseline value - baseline value

The number and the percentage of patients with notable vital signs will be presented. The criteria for notable vital sign abnormalities are provided in Table 2-3 below:

Table 2-8 Criteria for notable vital sign abnormalities

Vital signs (unit)	Normal measure	Notable abnormality
Systolic blood pressure (mmHg)	90 to <120 mmHg	>= 140 mmHg (hypertension) or < 90 mmHg (hypotension)
Diastolic blood pressure (mmHg)	60 to <80 mmHg	>= 90 mmHg (hypertension) or < 60 mmHg (hypotension)
Pulse (bpm)	60 to 100(bpm)	> 100 bpm (tachycardia) or < 60 bpm (bradycardia)

Note: Blood pressure indicative

- Hypertension if systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg
- Hypotension if systolic blood pressure of <90 mmHg and/or a diastolic blood pressure of <60 mmHg
- A blood pressure indicative of prehypertension (systolic blood pressure of 120 to <140 mmHg and/or diastolic blood pressure of 80 to <90 mmHg) will not be regarded as notable (Chobanian, Bakris, and Black 2003).

A listing of the newly-occurring notably abnormal vital sign will be provided.

All vital signs will be listed with “on-treatment” flag displayed.

2.9 Pharmacokinetic endpoints

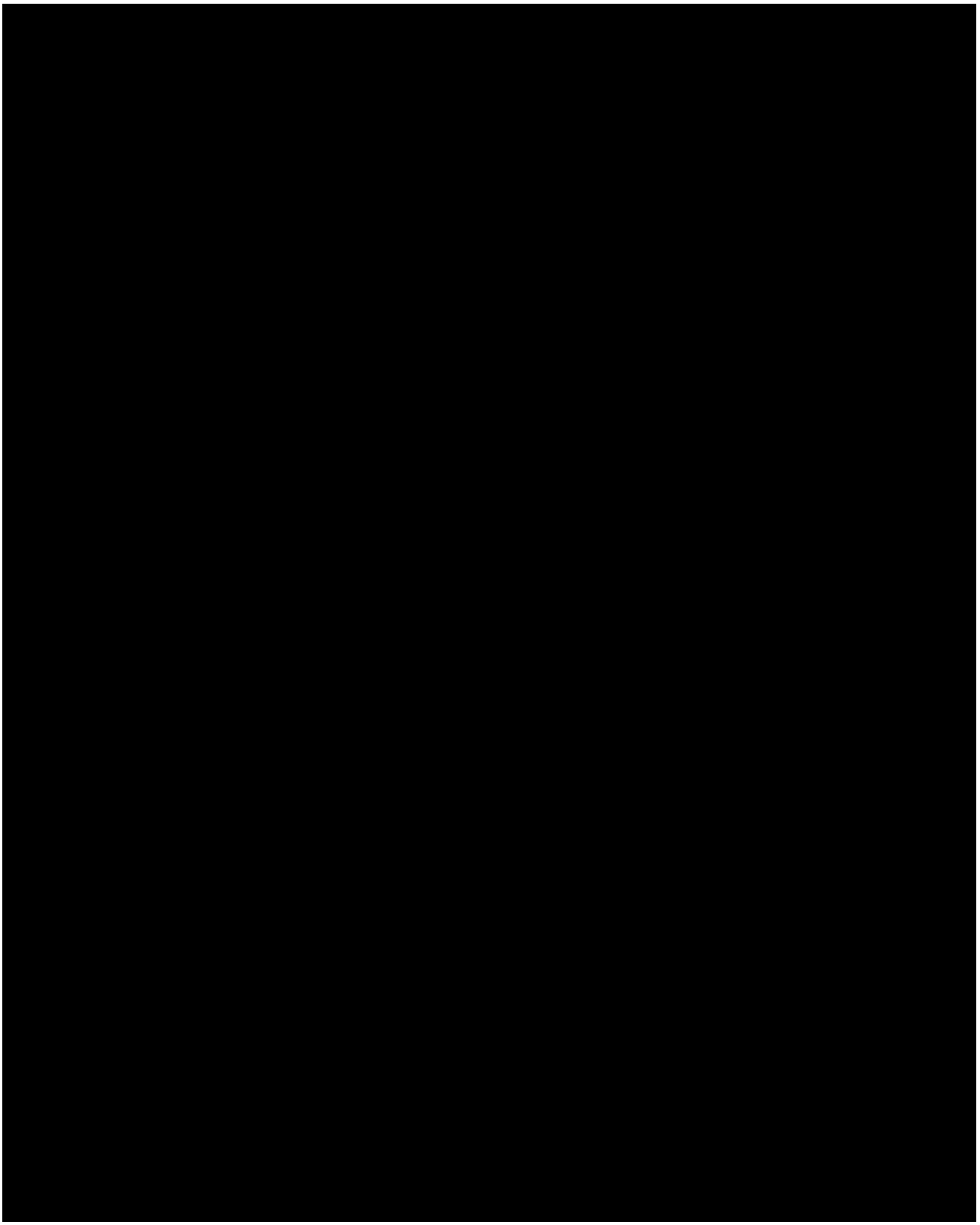
Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable.



2.14 Interim analysis

The database of this study will be locked twice, first after the end of double-blind treatment period (Week 12) and again at the end of the follow-up period (Week 53). Data analyses will follow each database lock. The main analysis for the primary objective will be done at Week 12. As Week 12 analysis considered primary and no specific hypothesis is pre-identified for testing, adjustment of significance level due to this interim analysis is irrelevant.

3 Sample size calculation

The table below considers total sample sizes of 75 patients (50 in secukinumab group and 25 in placebo group) and 99 patients (66 in secukinumab group and 33 in placebo group) to estimate the difference between the two groups with respect to the pooled estimate of the two percentages of patients who have the "event" at Week 12 for each of the two primary efficacy variables. The table shows "margin of error" (half-width of confidence interval) for a two-sided 95% confidence interval (Julious and Patterson, 2004; Kianifard and Islam, 2011; nQuery Advisor 7.0).

Based on the results in the above table, it was decided that approximately 75 randomized patients (50 in secukinumab group and 25 in placebo group) will be randomized in this exploratory study to estimate the difference in response rates between the two treatment groups.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

- The last day in the month and
- The calculated end day of the corresponding epoch

5.1.2 AE date imputation

Impute AE end date:

1. If the AE end date ‘month’ is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 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 (min (last visit date, last dose date + 84 days), 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.

Impute AE start date:

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

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).

2. Else AE start reference date = treatment 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 treatment start date year value, the AE started before 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 treatment start date year value, the AE started after 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 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 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 treatment start date month or greater than the 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.

5.1.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.

2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).

3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:

    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).

    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:

    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM starts date year value is equal to the treatment start date year value:

    a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.

    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).

c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

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

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.4 Other imputations

Only PASI [redacted] based response variables are imputed with multiple imputation or non-response, other response variables (e.g. DLQI 0 or 1 achievement) will be imputed with LOCF.

5.2 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote.

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in [redacted] at the path [redacted].

5.3 Laboratory parameters derivations

See Section 2.8.3.

5.4 Statistical models

5.4.1 Primary analysis

No formal hypothesis will be tested.

Treatment difference will be calculated in terms of proportion of response along with 95% CI using normal approximation of binomial distribution.

Sample SAS code:

```
proc freq order=data;
        weight Count;
        table Gender * Response / chisq riskdiff;
run;
```

Sensitivity analysis:

Sample SAS Code:

Logistic regression model with treatment and body weight (<90 kg, >=90 kg) as explanatory variables.

```
proc logistic data=xxx descending;
  class treatment weight/ param=glm ;
  model <response var> =treatment  weight;
  contrast 'trtA vs. trtB    '  treatment  1 -1  ;
 run;
```

Logistic regression model with treatment and body weight (<90 kg, >=90 kg) and treatment-by-body weight(<90kg, >=90kg) as explanatory variables.

```
proc logistic data=xxx descending;
  class treatment weight/ param=glm ;
  model <response var> =treatment  weight treatment*weight;
  contrast 'A vs B in wgt=1 (<90)' treatment 1 -1 treatment*wgt 1 0 -1 0
/estimate=exp;
  contrast 'A vs B in wgt=1 (>=90)' treatment 1  -1 treatment*wgt  0 1 0 -1
/estimate=exp;
run;
```

Note: 'descending' option is used if Yes is coded as 1 and No is coded as 0

if Yes is coded as 1 and No is coded as 2 then no option is requesired

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause patients to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Informed Consent not signed	Excluded from FAS and SAF	3
INCL02	Age criteria not met	Excluded from none of the analysis set	0
INCL03	Diagnosis of chronic plaque type psoriasis is within 6 months prior to Randomization	Excluded from none of the analysis set	0
INCL04	BSA is below 10% and PASI total score is below 12 [redacted] at visit 2	Excluded from none of the analysis set	0
INCL05	Subject with systemic therapy are not Inadequately controlled by topical Treatment and/or phototherapy and/or previous systemic therapy	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL01	Having psoriasis other than chronic plaque type psoriasis.	Excluded from none of the analysis set	0
EXCL02	Medication induced psoriasis or medication exacerbation psoriasis	Excluded from none of the analysis set	0
EXCL03	Previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA receptors.	Excluded from none of the analysis set	0
EXCL04	Diagnosis of other active ongoing skin diseases or skin infections (bacterial, fungal, or viral), or inflammatory diseases other than psoriasis that may interfere with the evaluation of psoriasis	Excluded from none of the analysis set	0
EXCL05	Ongoing use of treatments prohibited by the protocol	Excluded from none of the analysis set	0
EXCL06	Subjects with live vaccination within 6 weeks prior to randomization or any time during the study	Excluded from none of the analysis set	0
EXCL07	Use of any investigational treatment within 4 weeks prior to Randomization, or within a period of 5 half- lives of the investigational treatment prior to Randomization, whichever is longer.	Excluded from none of the analysis set	0
EXCL08	Currently enrolled in any other clinical trial involving any investigational agent or device	Excluded from none of the analysis set	0
EXCL09	Patients using cholesterol lowering medication who have not been on a stable dose for at least 90 days prior to randomization and who are unable to remain on a stable dose during the study.	Excluded from none of the analysis set	0
EXCL10	Pregnant or nursing (lactating) women	Excluded from none of the analysis set	0
EXCL11	Women of child-bearing potential not using effective methods of contraception during dosing of study treatment and for 16 weeks after stopping of study treatment.	Excluded from none of the analysis set	0
EXCL12	Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the patient unsuitable for the trial or puts the	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
	patient at increased risk.		
EXCL13	Underlying condition which, in the opinion of the investigator, significantly immunocompro mised the patient and/or places the patient at unacceptable risk for receiving an immunomodula tory therapy.	Excluded from none of the analysis set	0
EXCL14A	Subject randomized with signs of uncontrolled hypertension (greater than 180 systolic mmHg and Diastolic Blood pressure is greater than 95)	Excluded from none of the analysis set	0
EXCL14B	Presence of significant medical problems	Excluded from none of the analysis set	0
EXCL15	Serum creatinine levels are greater than 2.0mg/dL or fasting blood glucose level is greater than or equal to 150mg/dL at screening or hemoglobin A1c greater than or equal to 7% at screening.	Excluded from none of the analysis set	0
EXCL16	Total white blood cells count less than 2500 /ul or thrombocytes less than 1,00,000 /ul or neutrophils less than 1500 /ul or hemoglobin less than 8.5 g/dL at screening.	Excluded from none of the analysis set	0
EXCL17	Active systemic infections (other than common cold) during the two weeks before randomization	Excluded from none of the analysis set	0
EXCL18	History of active tuberculosis/lat ent tuberculosis after the protocol specified time.	Excluded from none of the analysis set	0
EXCL19	**Positive serology for human immunodeficien cy virus (HIV), hepatitis B or C infection at screening**	Excluded from none of the analysis set	0
EXCL20	History of lymphoprolifera tive disease / known malignancy / history of malignancy of any organ system within the past 5 years	Excluded from none of the analysis set	0
EXCL21	History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to Baseline.	Excluded from none of the analysis set	0
EXCL22	History of hypersensitivity to constituents of the	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
	study treatment and/or patients who are allergic to rubber or latex		
EXCL23	Medical and/or psychiatric and/or other condition which would preclude the patient from adhering to/ completing the protocol.	Excluded from none of the analysis set	0
EXCL24	Patients unable and/or not willing to self- administer secukinumab injections or who have no trained caregiver available to administer the injections	Excluded from none of the analysis set	0
TRT01	Results of serum pregnancy and/or urine pregnancy test is positive. However, medication is given.	Excluded from none of the analysis set	0
TRT02	Patient Withdrew consent. However, dose was administered.	Excluded from none of the analysis set	0
TRT03	Incorrect, study medication administered	Excluded from none of the analysis set	0
TRT04	incorrect route of administration of study drug at any time during the study, per protocol	Excluded from none of the analysis set	0
TRT05	Les than 2 injections of study drug administered	Excluded from none of the analysis set	0
TRT06	More than2 injections of study drug administered	Excluded from none of the analysis set	0
TRT07	Missed Dose	Excluded from none of the analysis set	0
COMD01	Use of prohibited treatment at any time during the study after randomization	Excluded from none of the analysis set	0
COMD02	Receipt of a live virus vaccination during the study	Excluded from none of the analysis set	0
WITH01	Patients voluntarily withdrew consent. However, still continuing in the study.	Excluded from none of the analysis set	0
OTH01	[redacted] or PASI assessment not performed	Excluded from none of the analysis set	0
OTH02	ICH-GCP non-compliance of study site in the study	Excluded from none of the analysis set	0
OTH03	Informed consent or process documentation deficiencies	Excluded from none of the analysis set	0
OTH04	Failure to perform key study procedures example [redacted] blood draw, IGA, PASI	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
OTH05	Wrong weight stratification data entered into IRT at randomization visit	Excluded from none of the analysis set	0

Protocol deviations will lead to subject classification into the analysis sets as follows:

Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3
FAS	1, 3

Population code text

Population Code	Population code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF

Unless otherwise stated, summary tables, figures and listings will be on all subjects included in the analysis set under consideration.

Table 5-2 Subject Classification

Analysis Set	PD ID that cause patients to be excluded	Non-PD criteria that cause patients to be excluded
RAN	NA	Not randomized
FAS	NA	Not in RAN; Mistakenly randomized and no double-blind study drug taken
SAF	NA	No double-blind study drug taken

Reference

Julious, S. and Patterson, S. (2004). Sample sizes for estimation in clinical research. Pharmaceut. Statist., 3(3), pp.213-215.

Kianifard, F. and Islam, M. (2011). A guide to the design and analysis of small clinical studies. Pharmaceut. Statist., 10(4), pp.363-368.

Stokes, M., Davis, C. and Koch, G. (2012). Categorical data analysis using the SAS system, third edition. Cary, NC: SAS Institute.