NOVARTIS

Clinical Development

AIN457A/Secukinumab®

CAIN457AUS02 / NCT02690701

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the effect of secukinumab on aortic vascular inflammation and cardiometabolic biomarkers after 12 weeks of treatment, compared to placebo, and up to 52 weeks of treatment with secukinumab in adult subjects with moderate to severe chronic plaque-type psoriasis

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09.02.2016	Prior to DBL		SAP first version 1.0 is created	Final version 1.0
20.06.2016	Prior to DBL	To keep consistency with latest protocol version	Family history of cardiovascular disease is added in page 12 In addition: 2) PASI and IGA response are changed to PASI and IGA score in page 12 ii) SAS code is updated in page 24 iii) Correction of typos iv) Protocol deviation list is updated	Section 2.3.3 Section 2.3.3 Section 5.4.1 Section 5.5 Section 2.1.1
16.5.2017	Prior to DBL	To keep consistency with standard analysis/ Master Analysis Plan	Addition of day of last dose of randomized study treatment Elaboration of duration of exposure and addition of visit window Re-modified the definition of Prior and concomitant medication Elaboration of handling of missing data and remodified the definition, as per protocol, of non-responder imputation Overall safety analysis specification	Section 2.4.1 Section 2.4.2 Section 2.7.3 Section 2.8 Section 2.7.2 and Section 4
29.5.2017	Prior to DBL	As discussed in Dry-run meeting with CTT	Cardiometabolic biomarker data will additionally be analyzed using stratified Wilcoxon rank sum test if the data does not satisfy normality condition One correction is made in notable criteria for pulse rate Spelling and format correction	Section 2.8.4.2
10.08.2017	Prior to DBL	As discussed with CTT	Visit window for target to background ratio and cardiometabolic biomarker data	Section 2.4.1.1
11.08.2017	Prior to	As discussed with CTT	Visit windows are updated	Section 2.4.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
	DBL			

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List of abbreviations

AE	Adverse event
ANCOVA	Analysis of covariance
BSA	Body Surface Area
CMB	Cardio metabolic biomarker
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDG-PET/CT	[18F]-fluorodeoxyglucose positron emission tomography with computer assisted tomography
GCP	Good Clinical Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IL	Interleukin
IRT	Interactive Response Technology
LLN	Lower Limit of Normal
LOCF	Last-observation-carried-forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PASI	Psoriasis Area and Severity Index
PFS	prefilled syringe
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
RAN	Randomized Set
SAF	Safety set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
s.c	Subcutaneous
TB	Tuberculosis
TBR	Target to background ratio
ULN	Upper Limit of Normal

1 Introduction

This statistical analysis plan (SAP) describes the statistical methodologies, which will be used in the phase IV clinical trial (CAIN457AUS02). This is a randomized, double blind, placebo- controlled, parallel group, multicenter study in adult subjects with moderate to severee chronic plaque-type psoriasis in the United States.

The purpose of this study is to evaluate the effect of secukinumab compared to placebo on aortic vascular inflammation and cardiometabolic biomarkers after 12 weeks of treatment, in subjects with moderate to severe plaque-type psoriasis. In addition, this study will evaluate the effect of longer-term treatment with secukinumab (up to 52 weeks) on aortic vascular inflammation.

1.1 Study design

In this study, there are four periods:

Screening: The screening period is between Week -4 to Baseline (B) visit, the duration of screening period will be up to four weeks (28 days).

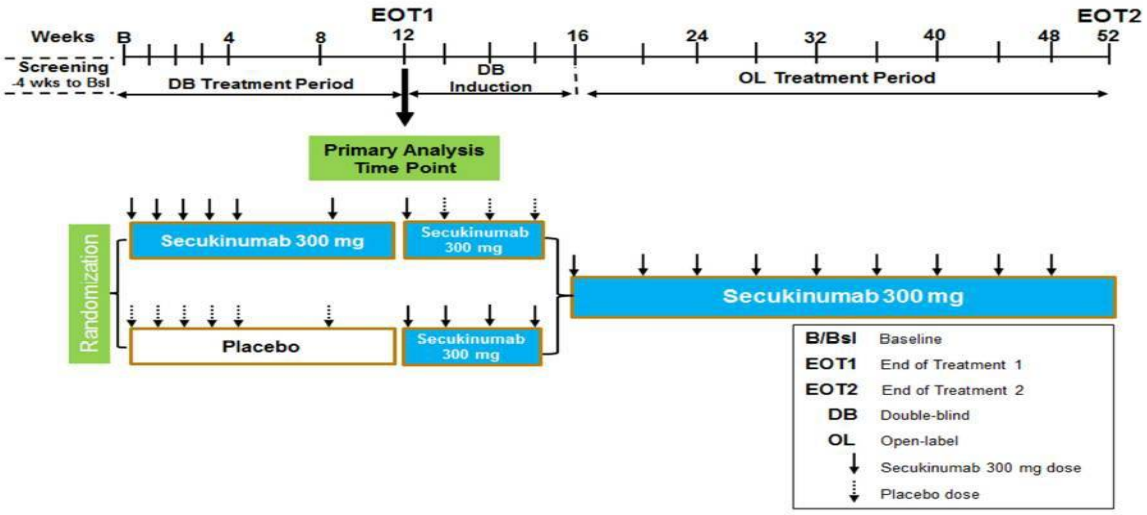
Double-blind Treatment Period: The double-blind treatment period is defined ad Randomization through Week 12 (prior to Week 12 dose), which is a total of 12 weeks time.

Double-blind Induction Period: The double-blind induction period is defined as the Week 12 dose through Week 15 dose, which is a total of 4 weeks time.

Open-label Treatment Period: The open-label treatment period is defined as the Week 16 though Week 52, which is a total of 36 weeks time.

Note: Baseline visit is Week 0 (Visit 2).

A schematic of the study design and visits is presented in figure below:



For more details, see study protocol, Section 3.1

All doses of study treatment will be self-administered. Self-administration of the study treatment refers to subject self-injection or injection by a trained caregiver regardless of whether self-administration occurs at the study site or at home.

Approximately 84 subjects with moderate to severe chronic plaque -type psoriasis will be randomized from approximately 10 investigative sites in the United States. Assuming a 20% screen failure rate, 105 subjects will need to be screened to provide the targeted number of randomized subjects. Subjects who drop out after they have been randomized will not be replaced.

At the start of the Double-blind Treatment Period, eligible subjects will be randomized via Interactive Response Technology (IRT) in a 1:1 ratio to one of two treatment groups (secukinumab 300 mg or placebo).

Assessments for the primary efficacy variable will be performed at Week 12 for both treatment groups prior to subjects receiving their Week 12 dose.

Primary analysis at Week 12 will be considered as the interim analysis. As Week 12 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

1.2 Study objectives

Primary objective

The primary objective is to evaluate the effect of secukinumab 300 mg s.c. compared to placebo on aortic vascular inflammation with respect to the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta. The primary analysis time point will be at Week 12.

Secondary objectives

- To evaluate the effect of secukinumab compared to placebo with respect to change from baseline in cardio metabolic biomarkers (cardio metabolic function [lipid particle size, HDL function (cholesterol efflux)], measures of inflammation [TNF-Alpha, IL-6, C reactive protein, GlycA], adiposity [leptin and adiponectin], insulin resistance [insulin levels/glucose to yield HOMA-IR], and markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A]) at Week 12

- To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to change from baseline in the PASI 75, 90 and 100 response rates at Week 12

- To evaluate the effect of secukinumab compared to placebo in subjects with moderate to severe chronic plaque-type psoriasis with respect to the Investigator's Global Assessment mod 2011 (IGA mod 2011) 0 or 1 response at Week 12

- To evaluate the effects of secukinumab compared to placebo with respect to change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 12

• To evaluate the clinical safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse event monitoring.

2 Statistical methods

2.1 Data analysis general information

Novartis Business Services 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.

At the Week 12 primary analysis time point, only the independent statistician and programmer(s) from Novartis will be unblinded in order to perform the interim analysis. The same SAP will be used for interim analysis.

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

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized as follows:

- for continuous variables, descriptive summary statistics (number of subjects, mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each visit will be reported by treatment group.

- for categorical variables, frequency and percentage will be presented at each time point by treatment group. Percentages will be calculated with respect to the number of subjects by treatment in the analysis set of interest.

2.1.1 General definitions

2.1.1.1 Study treatment

Secukinumab 300 mg (two s.c. injections of the secukinumab 150 mg dose) will be considered as study treatment throughout the study, which will be compared with placebo (two s.c. injections of 150 mg secukinumab matching placebo per dose).

The treatment groups and dosing frequency are described in Table 2-1 below:

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 Rand, Wks 1, 2, 3, 4 and 8	2x s.c. secukinumab 150 mg injection at Wk 12	2x s.c. secukinumab 150 mg injection at Wks 16 – 48
		2x s.c. secukinumab 150 mg PBO injection at Wks 13, 14 and 15	
Placebo (PBO)			
	2x s.c. secukinumab 150 mg PBO injection at Rand, 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 Wks 16 – 48

DB = Double-blind; OL = Open-label; Rand = Randomization; Wk = Week

2.1.1.2 Study day

The day of first administration of the double blind randomized treatment will be considered as study day 1. All other study day will be labeled relative to study day 1. The descriptor "study day 0" will not be used.

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, and 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.

2.1.1.3 Baseline and post-baseline assessments

Baseline assessments are defined as the last assessment before the first dose of double-blind randomized study treatment, which is typically the last assessment taken before study drug administration at Visit 2. If the baseline assessments are missing, then the last available measurement before the first dose of study treatment will be considered as baseline.

All the assessments after first dose of study treatment will be considered as post -baseline assessments. Therefore, Visit 3 and later visits will be considered as post-baseline visit.

Any procedure performed between Visit 1 and Visit 2 will be considered as screening assessment.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the CRF.

Duration of exposure is defined in Section 2.4.1.

If a subject discontinued early, then the last visit during the treatment period is considered (e.g., last visit in the induction period, if patient discontinued from the induction period) to calculate the duration of exposure.

On-treatment is defined as assessments within last dose plus 84 days.

2.2 Analysis sets

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

Randomized Set: The randomized set includes all subjects who were randomized.

Safety Set: The Safety Set includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received.

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

Rule for exclusion criteria from analysis sets: See Appendix 5-5.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

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

The number and percentage of subjects screened, randomized, completed study periods (treatment period 1 and treatment period 2), and discontinued the study prematurely including

the reason for discontinuation will be presented by overall and study periods for each treatment group for all screened subjects.

Patients withdrawing consent will be listed with reason for withdrawal.

The number and percentage of subjects with protocol deviations (see Appendix 5-5) will be tabulated by treatment and listed separately by treatment groups.

2.3.2 Demographics

The following demographic data collected at Visit 2 will be summarized by treatment for the Full analysis set and the Randomized set:

- age (in years)
- sex (male/female)
- race (Caucasian/black/Asian/native American/pacific islander/unknown/other)
- ethnicity (non-Hispanic or Latino/Hispanic or Latino)
- Child-bearing potential (able to bear child/post-menopausal/sterile - of child bearing age).

2.3.3 Baseline characteristics

The following baseline characteristics data will be summarized by treatment groups for the Full analysis set and the Randomized set:

Psoriasis history / Prior psoriasis therapies

Psoriasis history and prior psoriasis therapies collected at Visit 1 will be summarized by treatment group.

Duration of plaque psoriasis will be calculated as follows:

Date of Visit 1 – Date of first diagnosis of plaque psoriasis + 1.

This duration will be summarized descriptively.

The type of prior psoriasis therapy (biologic systemic therapy, non -biologic systemic therapy, topical, phototherapy, photochemotherapy) and the respective duration of exposures will be reported along with the reason of discontinuation of the therapy. This data will also be listed.

Smoking history

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

The subject'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 calculated as follows:

Date of Visit 1 – Date of last use of tobacco + 1. This duration will be summarized descriptively by treatment.

Alcohol use history

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

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

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

This duration will be summarized descriptively by treatment.

Comorbidities – cardiovascular history

Cardiovascular history will be summarized using frequencies and percentages by categories specified in the eCRF, ongoing status and treatment. Duration of cardiovascular diseases ongoing at Visit 1 will be summarized descriptively. Frequency and the percentage of the occurrence of each category will be presented. Also, frequency and percentage of ongoing cardiovascular disease will be presented. This data will also be listed.

In addition, family history of cardiovascular disease will be summarized descriptively. This data will also be listed.

Relevant medical history / Current medical conditions

Relevant medical history / current medical conditions will include data up to six months prior to signing of the informed consent and not including psoriasis or psoriatic arthritis and cardiovascular histories. Any condition entered on the relevant medical history / current medical conditions CRF will be coded using the MedDRA dictionary and summarized by System Organ Class (SOC) and Preferred Term (PT). This data will also be listed with ongoing treatments flagged.

Tuberculosis status

Presence of tuberculosis is assessed at Visit 1 which includes tuberculosis workup conducted (yes/no), result of workup (active, latent, no – tuberculosis diagnosed/present) and tuberculosis therapy started (yes/no). This data will be summarized by treatment.

Other baseline characteristics

In addition, the following variables collected at baseline will be summarized by treatment:

- height (in cm)
- weight (in kg)
- pulse (beats/min)
- blood pressure (mmHg)
- hematology
- clinical chemistry
- viral serology

  - HIV 1/2
  - Hepatitis B
  - Hepatitis C
- serum pregnancy
- PASI score
- IGA mod 2011 score
- DLQI total score

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

2.4.1 Study treatment exposure and compliance

The duration of exposure to study treatments will be presented based on safety set.

Duration of exposure is defined as the time from first dose of study treatment to the time of treatment switch (for subjects who switch treatment) or end of treatment period. For subjects who discontinue duration of exposure will be the last visit in the corresponding treatment period. For example if a subject discontinues during induction period, this will be the discontinuation date from induction period recorded on the induction period completion CRF page.

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 duration in days will be summarized by treatment, descriptively and using frequencies and percentages for categories: “≥4 weeks”, “≥12 weeks”, “≥16 weeks”, and “≥52 weeks”.`

More precisely, duration of exposure will be summarized for following categories:

“any exposure”, “≥1 week”, “≥2 weeks”, “≥3 weeks”, “≥4 weeks”, “≥8 weeks”, “≥12 weeks”, “≥16 weeks”, “≥28 weeks”, “≥40 weeks” and “≥52 weeks”.

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.

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% to 100%, by treatment.

2.4.1.1 Visit window

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. In the following tables, 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. E.g., if the Week 4 visit of a subject 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 subject 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.

Table 1-1 Assessment windows for PASI and IGA assessment:

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 day to Day 1
Week 4	4	29	Day 2-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-141
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

Table 1-2 Assessment windows for DLQI

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 day to Day 1
Week 12	12	85	Day 72-99
Week 24	24	169	Day 100-197
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

Note: Range of visit windows are discussed and agreed with CTT.

The analysis visit will be used for listing of visit and period for safety data.

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 subject 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. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Note: Target to background ratio (TBR) and cardiometabolic biomarker (CMB) data will be analyzed as per CRF visit. In CMB data analysis, if the patient is discontinued then the discontinued study visit will be mapped for analysis to the next visit of the last available assessment before discontinuation with in the same treatment period.

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 except DLQI, EQ-5D and health assessment, PGIC	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 (e.g. laboratory values, vital signs, 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 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	Notable abnormalities (e.g.	The most extreme measurement in the window

Timing of measurement	Type of data	Rule
and efficacy	vital signs, PGIC) and CTCAE grading for laboratory values	will be used. Note this means a subject can have a notably high and notably low measurement within a window
Post-baseline efficacy	FDG –PET scan	Data will be analyzed as per CRF captured visit
	Cardiometabolic biomarker	Data will be analyzed as per CRF captured visit but for discontinued patients only discontinued visit will be mapped to the next visit of the last available assessment before discontinuation within the same treatment period

2.4.2 Prior, concomitant and post therapies

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken, as follows:

Prior medication: Treatments taken and stopped prior to first dose of study treatment.

Concomitant medication: Any medication administered at least once between the day of first dose of randomized study treatment and the last day of study visit (including those which were started pre-baseline and continued into the treatment period), other than study medication, will be considered as concomitant medication.

Concomitant medications excluding tropical corticosteroid will be summarized.

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, concomitant medications will be summarized by treatment using frequency counts and percentages for Safety Set, in separate tables.

Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group. In addition, concomitant use of tropical corticosteroid will be summarized separately by treatment.

Treatment use for indication, 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.

2.5 Analysis of the primary objective

2.5.1 Primary efficacy variable

The primary efficacy variable is the change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta obtained via FDG-PET/CT

scans at Week 12. Baseline is defined as the target to background ratio at Visit 2. Patients will be included in the analysis if they have both baseline and post-baseline assessments.

TBRmax (in the dataset) at each visit will be used for analysis. The primary analysis will be based on Full Analysis Set.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment, baseline, and body weight (<90 kg, ≥90 kg) as explanatory variables.

Following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A):

$$H_0: \mu_1 - \mu_0 = 0$$

$$H_A: \mu_1 - \mu_0 \neq 0$$

where μ_1 and μ_0 denote the population mean of change from baseline in the target to background ratio from the aorta at Week 12 for secukinumab group and placebo group, respectively.

The least squares means of the two treatment groups, least squares mean difference , and 95% confidence interval for the difference in the two treatment groups will be presented along with the p-value based on the fitted linear model.

2.5.3 Handling of missing values/censoring/discontinuations

If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis.

2.5.4 Supportive analyses

A supportive nonparametric analysis will be performed to examine the consistency of results if the assumption of normality for the distribution of the primary efficacy variable is not tenable. For this supportive analysis, the primary efficacy variable will be analyzed using the stratified Wilcoxon rank-sum test with modified ridit scores (van Elteren's test), adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012). Supportive analysis will be based on Full Analysis Set.

In addition, changes from baseline in each of the five segments of aorta (ascending aorta, aortic arch, descending thoracic aorta, suprarenal abdominal aorta, infrarenal abdominal aorta) will be analyzed similar to the analyses of the primary efficacy variable.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objectives

Analyses of the secondary efficacy analysis will be based on Full Analysis Set.

2.7.1 Secondary efficacy variables

The secondary efficacy variables are the following:

- Change from baseline in each biomarker (specified in Section 2.7.2.1)
- PASI 75 response (yes, no)

- PASI 90 response (yes, no)
- PASI 100 response (yes, no)
- IGA mod 2011 score of 0 or 1 (yes, no)
- Change from baseline in DLQI total score

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Cardiometabolic Biomarkers

Change from baseline in each cardometabolic biomarker, described in Section 2.12, will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable.

In addition, change from the baseline in each biomarker will be analyzed using the stratified Wilcoxon rank -sum test with modified ridit scores (van Elteren's test), adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012) if the normality assumption for the variable is not tenable. The analysis will be based on Full Analysis Set.

2.7.2.2 Psoriasis Area and Severity Index (PASI)

PASI 75 / 90 / 100 responses will be analyzed at each time point using the Cochran-Mantel-Haenszel test to compare secukinumab and placebo, adjusting for body weight (<90 kg, ≥90 kg) (Stokes, Davis, and Koch, 2012). A 95% confidence interval for the difference between the two treatment groups in the proportion of subjects who are responders will be calculated using the normal approximation to the binomial distribution.

In addition, the PASI responses by visit will be summarized by treatment.

2.7.2.3 Investigator's Global Assessment (IGA mod 2011)

IGA mod 2011 (0 or 1) response will be analyzed at each time point using the Cochran-Mantel-Haenszel test to compare secukinumab and placebo, adjusting for body weight (<90 kg, ≥90 kg). A 95% confidence interval for the difference between the two treatment groups in the proportion of subjects who are responders will be calculated using the normal approximation to the binomial distribution. In addition, the IGA mod 2011 responses by visit will be summarized by treatment.

2.7.2.4 Dermatology Life Quality Index (DLQI)

Change from baseline in DLQI total score will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable. In addition, DLQI total score will be summarized by visit and treatment.

2.7.3 Handling of missing values/censoring/discontinuations

For continuous secondary efficacy variables with more than one post-baseline assessment (i.e. cardiometabolic biomarkers and DLQI score), missing data will be imputed using the last-observation-carried-forward (LOCF) method. Baseline value will not be carried forward. If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis.

For the subject who switch treatment after end of treatment period 1 (EOT 1), values of EOT1 are not carried forward to treatment period 2 (EOT 2).

For binary secondary efficacy variables (i.e. PASI 75,90,100 response and IGA mod 2011 0 or 1 response) at Week 12 (and other time points), a subject with a missing assessment will be considered as a responder (yes) if the subject meets the response criterion at the time of premature discontinuation from the study. Otherwise, the subject will be considered as a non-responder (no).

2.8 Safety analyses

Analysis of safety data will be based on the Safety Set.

Any adverse event will be coded using the MedDRA dictionary for the Safety Set.

Treatment groups for evaluation

The summaries of evaluation will be reported for treatment period 1 and entire treatment period, respectively.

The following groups will be used for treatment period 1:

- 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. Adverse events occurring after signing of informed consent but before first dose of study treatment and those occurring after 7 days of last study treatment (30 days for SAEs) will be listed only.

All adverse events will be coded using the MedDRA dictionary and summarized by system organ class and preferred term 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.

In addition following information will be listed by treatment group:

- Severity grade
- Relationship to the study treatment
- Duration
- Whether it constitutes a serious adverse event
- Action taken regarding study treatment
- Concomitant medication(s) taken or non-drug therapies given
- Outcome

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.

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 syste m organ class level.

All SAEs will be listed.

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

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

Any death occurring between study day 1 and last day of treatment exposure + 30 days will be summarized by system organ class and preferred term for each treatment group and listed along with primary reason for death. Death occurring in the screening period and after 30 days of last dose of study treatment will be flagged.

2.8.3 Laboratory data

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

change from baseline = post-baseline value – baseline value

For each variable, the maximum change (maximum decrease and maximum increase) from baseline, if appropriate for each study phase, will be analyzed analogously.

In addition, shift tables will be provided for all variables to compare a subject'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.

The expanded laboratory ranges and the clinically notable abnormalities of key laboratory variables are given below:

Table 2-2 Criteria for 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	> 1.5 x ULN
Renal function and electrolyte variables	
Creatinine (serum)	> 1.5 x ULN
Hematology values	
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

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. Change from baseline will be calculated only for the subjects 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 subjects with notable vital signs will be presented. The criteria for notable vital sign abnormalities are provided in Table 2-3 below:

Table 2-3 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: 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.

2.9 Pharmacokinetic variables

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Not applicable for this section.

2.12 Biomarkers

The following cardiometabolic biomarkers will be analyzed individually:

- cardiometabolic function [lipid particle size, HDL function (cholesterol efflux)]
- measures of inflammation [TNF-Alpha, IL-6, C reactive protein, GlycA]

- adiposity [leptin and adiponectin]
- insulin resistance [insulin levels/glucose to yield HOMA-IR]

markers predictive of diabetes [apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A]

The analysis method is given in section 2.7.2.1.

2.14 Interim analysis

The primary analysis at Week 12 will be considered as interim analysis. As Week 12 is the primary analysis time point, no adjustment to the significance level of 0.05 will be made.

3 Sample size calculation

The sample size was based on change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio (TBR) from the aorta. Using a t-test, a clinically important mean treatment difference of 0.15, a (common) standard deviation (SD) of 0.196, an allocation ratio of 1:1, a two-sided significance level of 0.05, and a power of 0.90, it was determined that approximately 74 subjects (37 in each treatment group) are necessary (nQuery Advisor 7.0) (Bissonnette et al, 2013; Tawakol et al, 2013). Without adjusting for multiplicity, the sample size of 74 subjects will also provide at least 0.90 power for other biomarkers if the treatment difference is 0.76 SD or smaller. The general threshold for clinical importance is 1 SD. Allowing for a loss to follow-up rate of 0.10, approximately 84 subjects (42 in each treatment group) will be randomized.

4 Change to protocol specified analyses

Missing data will not be imputed using last-observation-carried-forward (LOCF) method for primary efficacy variable, since there is only one post-baseline visit.

For continuous secondary efficacy variables with more than one post-baseline assessment, missing data will be imputed using multiple imputation (in addition to LOCF).

For cardiometabolic biomarker, if the normality assumption is not tenable, additionally data will be analyzed using stratified Wilcoxon rank sum test.

5 Appendix

This section will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 AE date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain	**NC** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start	**(C)** Before Treatment Start
YYYY = TRTY	**(B)** Uncertain	**(C)** Before Treatment Start	**(A)** Uncertain	**(A)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start	**(A)** After Treatment Start

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial, AE end date > = Treatment start date or AE is ongoing, then AE start reference = treatment start date.

Relationship		Time imputation
Before AE start reference	Partial date indicates AE start date prior to AE start reference	
After AE start reference	Partial date indicates AE start date after AE start reference	
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start reference	
Imputation Calculation		
NC/Blank	No convention	
(A)	MAX(01MONYYYY, AE start reference+1 day)	
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	
Complete date	No date imputation	If time is captured for the study Case1: if AE start date is not equal to AE start reference then do the following: If minutes missing then AESTMF = M and time is imputed to hh:00 If minutes missing then AESTMF = H and time is imputed to 00:00 Case2: if AE start date = AE start reference then AESTMF = H and time is imputed to treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date

Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing

Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. if AE end date is not equal to Treatment end date, then do the following:

if minutes missing then time is imputed to hh:00 if time missing then time is imputed to 00:00

Case 2: if AE end date = Treatment end date then time is imputed to treatment end time

If the AE end date is partial then end time is imputed to 00:00.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y
else if month of the imputed date is not equal to MON then date flag = M
else if day of the imputed date is not equal to day of original date then date_flag = D
else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H
else if minutes of the imputed time is not equal to minutes of original time then time flag = M
else time flag = null.

5.1.2 Concomitant medication date imputation

This algorithm is used when *event* is the partial start date of the concomitant medication. The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(C2)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain
YYYY < TRTY	**(D)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start
YYYY = TRTY	**(C2)** Uncertain	**(A)** Before Treatment Start	**(C1)** Uncertain	**(B)** After Treatment Start
YYYY > TRTY	**(E)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start	**(B)** 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
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ' ' THEN TRTSDT+1
(D)	01JULYYYY

(E)	01JANYYYY

Concomitant Medication End Date Imputation

If not ongoing then -

Imputed date = date part of CMENDTC, if complete date

Imputed date = min(completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min(completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

Concomitant Medication Date Flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.1.2.1 Prior therapies date imputation

Same as above

5.1.2.2 Post therapies date imputation

Same as above

5.1.2.3 Other imputations

Same as above

5.2 AEs coding/grading

NA

5.3 Laboratory variables derivations

NA

5.4 Statistical models

5.4.1 Primary analysis

ANCOVA model for change from baseline in the target (arterial vascular uptake) to background (venous blood pool) ratio from the aorta at Week 12

Change = intercept+ treatment + body weight stratum (<90kg, ≥90 kg) + baseline value + error.

The SAS procedure MIXED will be used with the following code:

```
proc mixed  data=<….>;
  class trtmnt bws;
  model change = trtmnt bws blv;
  lsmeans  trtmnt / cl diff;
```

```
run;
```

where

chnage = change from the baseline at Week 12
trtmnt = Treatment
bws = body weight stratum (< 90 kg,>= 90kg)
blv= baseline value .

Results will be presented with raw mean and standard error of the baseline value, with least squares mean and standard error for treatment effects and least squares mean, standard error, associated two-sided 95% confidence interval, and two-sided p-value for the treatment contrast.

A Q-Q plot will be performed to check the normality of primary variable.

5.4.1.1 Supportive analysis

Stratified Wilcoxon rank-sum test will be performed and implemented in SAS using **PROC FREQ** with **CHM2 SCORES = MODRIDIT** option.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Table 5.1 Protocol deviations that cause subjects to be excluded from analysis

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Patients have not signed Informed Consent Form prior to initiation of any study-related procedure.	Excluded from FAS and SAF	3
	Age criteria not met	Excluded from none of the analysis set	0
INCL0	Date of diagnosis of plaque psoriasis is greater than or equal to 6 months prior to randomization	Excluded from none of the analysis set	0
INCL0	No Moderate to severe plaque psoriasis at Baseline Visit	Excluded from none of the analysis set	0
INCL0	Subject with systemic therapy are not inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy for Plaque psoriasis.	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL06	Physical examination, FDG-PET/CT scan without clinically significant findings, clinical laboratory results within laboratory ref ranges or abnormal results are deemed to be not clinically significant.	Excluded from none of the analysis set	0
EXCL01	Forms of 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 targeting IL-17A or the IL-17RA	Excluded from none of the analysis set	0
EXCL04	Diagnosis of other ongoing active skin diseases or skin infections or inflammatory diseases other than psoriasis.	Excluded from none of the analysis set	0
EXCL05	Unwillingness to limit UV light exposure (sunbathing and/or use of tanning devices)	Excluded from none of the analysis set	0
EXCL06	Prohibited medications used/washout period not observed/Other treatments known to worsen psoriasis not stable for 4 weeks before randomization	Excluded from none of the analysis set	0
EXCL07	Use of Other investigational drugs within 5 half-lives or 4 weeks prior to randomization, whichever is longer	Excluded from none of the analysis set	0
EXCL08	Use of unstable dose of cholesterol-lowering medications for at least 90 days prior to randomization	Excluded from none of the analysis set	0
EXCL09	Pregnant or Nursing (lactating) women at randomization and/or any post-randomization visit.	Excluded from none of the analysis set	0
EXCL10	Women of childbearing potential who do not agree to be compliant with protocol-specified contraception during the study	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL11	Current and/or uncontrolled underlying condition(s) which in the judgement of investigator renders the patient unsuitable for the study.	Excluded from none of the analysis set	0
EXCL12	Current and/or uncontrolled significant medical problems	Excluded from none of the analysis set	0
EXCL12A	Subject randomized with signs of uncontrolled hypertension (≥180 systolic/ 95 diastolic mmHg)	Excluded from none of the analysis set	0
EXCL12B	Subject randomized with signs of uncontrolled hypertension (≥180 systolic/ 95 diastolic mmHg)	Excluded from none of the analysis set	0
EXCL13	Serum creatinine levels are greater than 2.0mg/dL or fasting blood glucose level is greater than or equal to 150mg/dL or hemoglobin A1c greater than or equal to 7% at screening.	Excluded from none of the analysis set	0
EXCL14	Total white blood cells count less than 2500 /ul or thrombocytes less than 1,00,000 /ul or neutrphils less than 1500 /ul or hemoglobin less than 8.5 g/dL at screening	Excluded from none of the analysis set	0
EXCL15	History of lymphoproliferative disease/ any known malignancy/ history of malignancy of any organ system in past 5 years	Excluded from none of the analysis set	0
EXCL16	History of active tuberculosis/latent tuberculosis after the protocol specified time	Excluded from none of the analysis set	0
EXCL17	Past or ongoing medical history record of HIV, hepatitis B or hepatitis C prior to screening	Excluded from none of the analysis set	0
EXCL18	Current and/or uncontrolled underlying condition(s) which significantly immunocompromises and/or places a patient at risk, in the Investigator's opinion	Excluded from none of the analysis set	0
EXCL19	Active systemic infections (other than common cold) during the two weeks before	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
	randomization		
EXCL20	Subjects with live vaccination within 6 weeks prior to randomization or any time during the study	Excluded from none of the analysis set	0
EXCL21	Presence of a medical or psychiatric condition that renders subject unable to adhere to protocol/complete the study	Excluded from none of the analysis set	0
EXCL22	History or evidence of drug or alcohol abuse within the 12 months prior to screening.	Excluded from none of the analysis set	0
EXCL22A	History or evidence of not willing to limit alcohol use to less than or equal to 14 drinks per week within 4 weeks prior to screening or anytime during the study.	Excluded from none of the analysis set	0
EXCL23	History of hypersensitivity to constituents of study treatment and/or allergic to rubber or latex	Excluded from none of the analysis set	0
EXCL24	Subjects who are not able 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	Incorrect, missed or partial doses of study medication administered by subject	Excluded from none of the analysis set	0
TRT02	Incorrect study drug administered at any time during the study	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
OTH01	Missing psoriasis efficacy assessment at any endpoints (IGA, PASI)	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 process or documentation deficiencies	Excluded from none of the analysis set	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
OTH04	First drug administration and/or Date of Visit 2 is not within 7 days of Baseline (Visit 2) FDG-PET/CT scan	Excluded from none of the analysis set	0
OTH05	Failure to perform key study procedures (example FDG-PET/CT scan, cardiometabolic biomarker blood draw)	Excluded from none of the analysis set	0
WITH1	ICF withdrawn but patient continuing in the study	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 subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAN	NA	Not randomized
FAS	As mentioned in table 5.1	Not in RAN; Inappropriately randomized
SAF	As mentioned in table 5.1	No double-blind study drug taken

6 References

Bissonnette R et al. (2013) Effects of the tumor necrosis factor-α antagonist adalimumab on arterial inflammation assessed by positron emission tomography in patients with psoriasis: results of a randomized controlled trial. Circ Cardiovasc Imaging; 83-90.

Chobanian AV, Bakris GL, Black HR (2003) Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension; 42:1206–52.

Stokes ME, Davis CS, Koch GG (2012) Categorical data analysis using the SAS system. 3rd ed; Cary, NC: SAS Institute, Inc.

Tawakol A, et al. (2013) Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multi-center FDG-PET/CT feasibility study. JACC; 909-17.

[AIN457A efficacy MAP M3 Amendment 5], available in Cabinets//CREDI Projects /A/AIN457A/Administrative files/CIS (Clinical Information Sciences)/Biostatistics

[AIN457 safety MAP M3 Amendment 4], available in Cabinets//CREDI Projects/A/AIN457A /Administrative files/CIS (Clinical Information Sciences)/Biostatistics