NOVARTIS

Clinical Development

Secukinumab, AIN457

CAIN457AFR01 / NCT02595970

A 52-week (plus extension until commercialization), single-arm study to evaluate psoriasis severity and its psychosocial impact using the Simplified Psoriasis Index at 16 weeks, as well as long-term safety, tolerability and efficacy of secukinumab administered subcutaneously in patients suffering from moderate to severe psoriasis

Statistical Analysis Plan (SAP)

Author: [redacted]

Document type: SAP Documentation

Document status: Final version 1.0

Release date: 10-Apr-2017

Number of pages: 28

Document History

Version	Date	Change
Final v1	*10-APR-2017*	

Table of contents

List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area under the curve
BISF-m	Brief Index of Sexual Functioning for men
BISF-w	Brief Index of Sexual Functioning for woman
BMI	Body mass index
BSA	Body surface area
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computerized tomography
DBL	Database lock
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
EOE	End of Extension
EOT	End of Treatment
FAS	Full Analysis Set
i	Intervention
IGA	Investigator's Global Assessment
IS	Included Set
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NovDTD	Novartis Drug and Therapy Dictionary
p	Psychosocial
PASI	Psoriasis Area and Severity Index
PFS	Pre-filles syringe
PLS	Product Lifecycle Service
PPS	Per Protocol Set
proSPI	Professionally-administratored Simplified Psoriasis Index
PT	Preferred term
QFT	QuantiFERON®-TB
ROC	Receiver Operating Characteristic
s	Severity
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
saPASI	Self-administratored Psoriasis Area and Severity Index
saSPI	Self-administratored Simplified Psoriasis Index
SD	Standard deviation
SE	Standard error
SOC	System organ class

SPI	Simplified Psoriasis Index
TEAE	Treatment-emergent adverse events

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical methods planned in Section 9 of the study protocol version 5 of phase IIIb clinical trial CAIN457AFR01 along with any additional analyses, specifications or deviations from this protocol planned before database lock (DBL). Determination of sample size is specified in Section 3.

This document is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report after the analysis has taken place.

1.1 Study design

This is an open-label multicenter, single arm study in 120 patients with moderate to severe psoriasis. There will be no randomization nor interim analysis for this study.

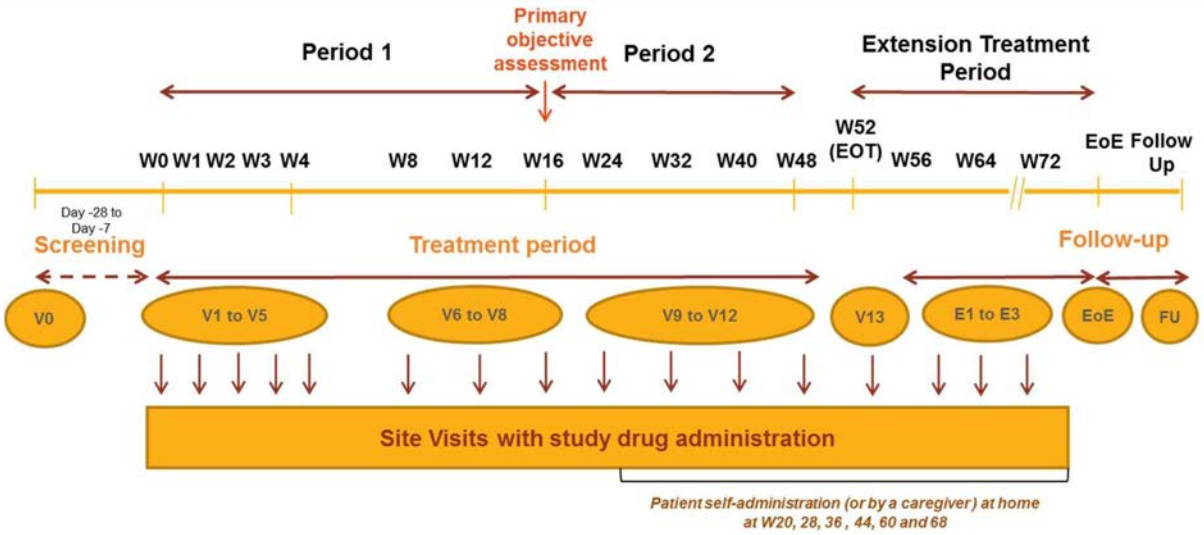
The study consists of five epochs:

- Screening to occur between day -28 and day -7
- Treatment
  - Treatment period 1
  - Treatment period 2
- Extension treatment period
- Follow-up

There will be an initial induction phase (5 weekly injections) before switching to monthly injections until Week 16. The patient will continue with monthly injections until Week 48 in case of a favorable response to treatment at Week 16. Patients who are deemed to be benefiting from the study drug after 48 weeks of treatment could be continuously treated until 3 November 2016 or until commercialization of Cosentyx® in France, whichever occurs first.

An illustration of the study design is depicted in Figure 1.1.

Figure 1-1 Study design



1.2 Study objectives and endpoints

1.2.1 Primary objective

The primary objective is to evaluate the benefit of secukinumab on the severity of psoriasis based on the Simplified Psoriasis Index (SPI). This index comprises 3 components: severity (s), psychosocial (p), and intervention (i). All components of SPI will be evaluated by both the physician (proSPI) and the patient (self-assessed: saSPI). Only the severity component will be evaluated for the primary objective , i.e. both proSPI (s) and saSPI (s).

1.2.2 Secondary objectives

Key secondary objectives are:

- to assess Psoriasis Area and Severity Index (PASI) weekly from week 0 to 4 then every 4 to 8 weeks until Week 56
- to evaluate correlation between PASI and proSPI (s)

Other secondary objectives include:

- to assess proSPI (s, p and i) over time (weekly from Week 0 to Week 4 then every 4 to 8 weeks until Week 56).
- to assess saSPI (s, p and i) over time (weekly from Week 0 to Week 4 then every 4 to 8 weeks until Week 56).
- to assess Dermatology Life Quality Index (DLQI) over time (weekly from Week 0 to Week 4 then every 4 to 8 weeks until Week 56).
- to assess self-administered PASI (saPASI) (weekly from Week 0 to Week 4 then every 4 to 8 weeks until Week 56).
- to assess pain, itching, and scaling using the Psoriasis Symptom Diary questionnaire over time (weekly from Week 0 to Week 4 then every 4 to 8 weeks until Week 56).

- to evaluate correlation between proSPI (for each component separately: s, p, i) and DLQI
- to evaluate correlation between proSPI (p, i separately) and PASI
- to evaluate safety during the treatment period (until the Week 52) and during the extension treatment period (after the Week 52)

1.2.3 Exploratory objectives

- to evaluate correlation between saSPI (s, p, i separately) and DLQI.
- to evaluate correlation between proSPI (s, p separately) and saSPI (s, p separately).
- to evaluate correlation between saSPI (s) and PASI.
- to evaluate the ability of SPI to discriminate between responders and non-responders based on PASI response.
- to explore sexual dysfunction using the Brief Index of Sexual Functioning for men/woman (BISF-m or BISF-w) questionnaire in a subset of subjects willing to complete sexual function questionnaire.

2 Statistical methods

2.1 Data analysis general information

The analysis will be performed by Novartis. The statistical software used for the analyses will be SAS version 9.4 or later.

Descriptive statistics for continuous variables in the study will include the number of observations, mean, standard deviation (SD), median, minimum, and maximum. The following number of decimal places will be used: mean, and median, values to 1 more decimal place than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data.

For categorical variables frequency and percentage will be presented for non-missing data.

If appropriate, 95% Confidence Intervals (CIs) will be presented along with p-values.

Unless otherwise specified, all statistical tests will be two-sided and will use the 5% level of significance.

All data will be listed by patient unless stated otherwise.

2.1.1 General definitions

2.1.1.1 Study treatment

The investigational drug, secukinumab, is to be injected subcutaneously and will be provided by Novartis in pre-filled syringes (PFS) of 150 mg. Two injections will therefore be necessary to obtain the required dosage of 300 mg.

2.1.1.2 Study day

The day of first administration of the treatment will be considered as study day 1. All other study day 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

The day before study day 1 will be calculated as:

date of event – date of first dose

2.1.1.3 Baseline and post-Baseline

Baseline data will be defined as the last available non-missing data collected prior to the first study treatment administration. Data collected after first dose of study treatment will be considered as post-Baseline data.

Change from Baseline will only be summarized for patients with both Baseline and post-Baseline unless stated otherwise, and it will be calculated as:

post-Baseline value – Baseline value

Correspondingly, percentage change will be calculated as:

100 * (post-Baseline value – Baseline value) / Baseline value

2.1.1.4 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 in this study are shown in Table 2-1. In this table, the days are counted since the first dose of study treatment. These visit windows apply to measurements taken at every visit. When visit windows are used, all visits (except follow up 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. If two visits fall into one window then the visit closest to target scheduled day will be analysed for that visit. Follow up visits will not be re-aligned.

Table 2-1 Assessment windows for scheduled visits

Visit	Week	Scheduled day	Visit Window
Baseline	0	1	-28 days to day 1
Visit 2	1	8	Day 2-11
Visit 3	2	15	Day 12-18
Visit 4	3	22	Day 19-25
Visit 5	4	29	Day 26-43
Visit 6	8	57	Day 44-71
Visit 7	12	85	Day 72-99

Visit	Week	Scheduled day	Visit Window
Visit 8	16	113	Day 100-141
Visit 9	24	169	Day 142-197
Visit 10	32	225	Day 198-253
Visit 11	40	281	Day 254-309
Visit 12	48	337	Day 310-351
Visit 13	52	365	Day 352-379
Extension 1	56	393	Day 380-421
Extension 2	64	449	Day 422-477
Extension 3	72	505	Day 478-533
Follow-up	80	561	≥ Day 534

2.1.1.5 Follow up visit

Efficacy data collected at follow up visits will not be summarized.

Efficacy data collected at follow up visits will be listed.

2.1.1.6 Unscheduled visit

All safety and exposure to study treatment data collected at unscheduled visits will be summarized.

Efficacy data collected at unscheduled visits will be visit windowed as per section 2.1.1.4 and will be presented in the same manner as scheduled visits.

All data collected at unscheduled visits will be listed.

2.2 Analysis sets

The following analysis sets will be used in this study:

Included Set (IS): The included set will comprise all patients included in the study. A patient is considered to be included in the study if he/she successfully completes the screening period. Completion of screening period is defined as patient who has "Will the subject continue into the Treatment phase?" equal to "Yes" from the *Screening Phase Disposition* eCRF page.

Full Analysis Set (FAS): The FAS will comprise all patients in the IS who are administered with at least one dose of investigational drug with at least one Baseline and one post-Baseline SPI evaluation.

The primary analysis will be performed on the FAS.

Safety Analysis Set (SAF): The SAF will comprise all patients in the IS who are administered with at least one dose of investigational drug during the treatment period.

Per Protocol Set (PPS): The PPS will comprise all patients in the FAS without any major protocol deviation.

Analysis sets for specific outputs are given in Table 2-2.

Table 2-2 Analysis data sets for specific outputs

Table	IS	FAS	SAF	PPS
Concomitant medication			x	
Demographics and Baseline characteristics	x			
Exposure			x	
Medical history	x			
Other efficacy analyses		x		
Patient disposition	x			
Patient reported outcomes		x		
Primary and key secondary efficacy variables		x		x
Protocol deviations	x			
Safety analyses			x	

The number and percentage of patients in each analysis set will be summarized based on the IS.

If protocol deviations (PDs) occur, then the data from specific patients, visits, or evaluations may be excluded from analysis. The criteria and determination of clinically significant PDs leading to exclusion from PPS will will be finalized prior to DBL and analysis.

2.2.1 Subgroup of interest

N/A

2.3 Patient disposition, demographics and other Baseline characteristics

2.3.1 Patient disposition

Patient disposition will be presented in listings.

The total number and percentage of subjects passing and failing screening be presented.

The number and percentage of patients who completed study periods (treatment period 1, treatment period 2, and extension treatment period) or discontinued the study prematurely including the reason for discontinuation will be presented by study periods for all subjects in the IS.

A schematic diagram of subject disposition will be provided.

2.3.2 Protocol deviations

The number and percentage of subjects with PDs will be tabulated by deviation category. A table with only major PDs and criteria leading to exclusion from analysis sets will also be presented. In both tables, subjects with multiple PDs will only be counted once at each level of summarization.

In addition, a listing of PDs will be produced including the accompanying deviation code.

Classification of which PDs will lead to exclusion from analysis sets will be agreed and documented in a data review meeting prior to database lock.

2.3.3 Demographics and other Baseline characteristics

Descriptive statistics for the following data and will be provided (including Baseline values of the main efficacy endpoints) for the IS population.

Demographics and background characteristics:

- age (in years, and year categories ≤ 65, > 65)
- gender (male/female)
- child bearing status (able to bear children/post menopausal/sterile - of child bearing age)
- race (Caucasian/Black/Asian/native American/Pacific islander/other)
- smoking status (never/current/fomer)
- average pack year (former/current/overall)
- height (cm)
- weight (kg)
- body mass index (BMI) = weight (kg) / (height (meters))^2
- sitting pulse (bpm)
- systolic and diastolic blood pressure (mmHg)
- pregnancy test (negative/positive/not done/unknown)
- education level (none/primary education/secondary education/university)

Disease history and Baseline disease characteristics:

- total body surface area (BSA) affected
- Baseline PASI
- time since diagnosis of plaque type psoriasis (years)
- Baseline Investigator Global Assessment (IGA)
- Baseline saPASI
- previous exposure to psoriasis therapy

The following data will also be summarized:

- standard 12-lead Electrocardiogram (ECG) at Baseline.
- QuantiFERON®-TB Gold In-Tube assay (QFT) at screening (positive / negative / indeterminate)
- X-ray (or Magnetic resonance imaging (MRI), computerized tomography (CT) scan) at screening

2.3.4 Medical history and current medical conditions

Analysis of medical history and current medical conditions will be based on the IS. General medical history, and current medical conditions collected in the CRF will be coded using the

Medical Dictionary for Regulatory Activities (MedDRA) dictionary. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary.

Psoriasis specific medical history will be summarized by predefined types of psoriasis collected on the CRF where the number and percentage of patients with each type will be presented. In addition, time since diagnosis will be summarizied for the following catogeries:
≤ 1 year, > 1 and ≤ 5 years, < 5 and ≤ 10 years, < 10 and ≤ 20 years, and > 20 years.

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

2.4.1 Study treatment

The analysis of study treatment data will be based on the SAF.

Duration of exposure is defined as the time from first dose of study treatment to the time of end of study day. For subjects who discontinue this will be the last visit in the corresponding treatment period. The duration of exposure to study treatments (days) will be calculated as:

end of study date – start date of study treatment + 1

The duration in days will be summarized using frequencies and percentables for categories: ≤ 4 weeks, > 4 ≤ 16 weeks, > 16 ≤ 52 weeks, > 52 ≤ 72 weeks, and > 72 weeks.

The number of percentage of subjects with dose amount < 300mg, 300mg, and > 300mg will be provided.

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. Prior (or previous) medication is defined as a treatment taken but stopped prior to first administration of investigational drug. Concomitant medication is any medication administered at least once between the day of first injection of investigational drug and the last day of study visit, including a medication initiated pre-screening and ongoing at the start of the treatment period.

Medications will be identified using the Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized for the SAF.

Prior and concomitant medications will be summarized in separate tables. They will be presented for the whole study period.

Medications will be presented in alphabetical order, by PT and grouped by anatomical main group. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular PT and at least one treatment in a particular anatomical main group.

By-patient listings for prior and concomitant medications will be provided.

Prior psoriasis therapy will be summarized overall, by type and PT.

2.5 Analysis of the primary objective

The primary objective is to evaluate the benefit of secukinumab on the severity of psoriasis based on the severity component of the SPI at Week 16.

2.5.1 Primary endpoint

The co-primary variables are:

- change from Baseline in proSPI (s) Week 16
- change from Baseline in saSPI (s) at Week 16

The primary analysis will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The following hypothesis will be tested for each co-primary endpoint at the 5% significance level (2-sided):

$$H_0: \mu_d = 0$$

$$H_A: \mu_d \neq 0$$

where μ_d denotes the mean difference of paired observations.

To assess the primary objective, the absolute change from Baseline in proSPI (s) and absolute change from Baseline in saSPI (s) will be analyzed using a paired t-test (Week 16 vs Baseline).

The key assumptions underlying the use of a paired t-test will be checked. In the event the data is non-normal, Wilcoxon signed rank test will be performed.

An adjustment for multiplicity will be performed using the Hochberg procedure and the family-wise type-I-error will be set to α=5% (2-sided). The adjustment will be applied as follows; if the maximum of the two p-values is rejected at the 5% level (2-sided) then both hypotheses are rejected and statistical significance is claimed for both endpoints. Otherwise if the maximum of the two p-values is not rejected, then the minimum p-value is tested at the 2.5% level (2-sided), if rejected then statistical significance is claimed only for this endpoint.

Descriptive statistics of proSPI (s) and saSPI (s) (Baseline, actual value, absolute and percentage change from Baseline) will be presented by visit for severity score and its components 1A and 1B. The number and percentage of reponses for 1A will be presented by body part. The change from Baseline of proSPI (s) and saSPI (s) will be presented graphically, showing the mean and SE of the change per visit.

The number and percentage of proSPI (s) and saSPI (s) will be presented by visit and by the following score bands: from 0 to 10, > 10 and ≤ 20, > 20 and ≤ 30, > 30 and ≤ 40, > 40 and ≤ 50. Graph of reponse distribution of proSPI (s) and saSPI (s) will be presented by the aforementioned score bands at Week 16.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will be imputed using Last Observation Carried Forward (LOCF) method. This approach will consist of replacing the missing Week 16 assessment by the last non-missing assessment value.

2.5.4 Supportive/sensitivity analyses

To assess for robustness of the results, the same analysis as specified in Section 2.5.2 will be repeated for the FAS (on observed data).

The primary analysis for the two co-primary endpoints will be also be performed on the PPS.

2.6 Analysis of the key secondary objective

The key secondary objectives of this study are:

- to assess PASI weekly from week 0 to 4 then every 4 to 8 weeks until end of study
- to evaluate correlation between PASI and proSPI (s)

2.6.1 Key secondary endpoint

The key secondary variables are:

- absolute PASI score values at each post-Baseline visit until end of study
- the correlation coefficient between PASI and proSPI (s) at each post-Baseline visit

The key secondary endpoints analyses will be based on the FAS (observed data only).

2.6.2 Statistical hypothesis, model, and method of analysis

Descriptive statistics of PASI score (Baseline, actual value, absolute change and percentage change from Baseline) will be presented by visit. The percentage change from Baseline of these scores will be presented graphically, showing the mean and SE of the percentage change per visit. The number and percentage of PASI score will also be presented by body region, symptom, and visit.

The number and percentage for each PASI response category (PASI 50 responders, PASI 75 responders, PASI 90 responders, and PASI 100 responders) will be presented by visit. For example, PASI 50 responders are the patients achieving ≥ 50% improvement (reduction) in PASI score compared to Baseline.

Change from Baseline to Week 16 of PASI score will be analyzed as for the primary analysis described in Section 2.5.2.

For the evaluation of the correlation between PASI and proSPI (s) at each post-Baseline visit using Spearman's correlation coefficient. Scatterplots of PASI and proSPI(s) at Week 16 will also be provided.

2.6.3 Handling of missing values/censoring/discontinuations

Analysis and presentations of key secondary objectives will only be based on observed data.

2.6.4 Supportive/sensitivity analyses

N/A

2.7 Analysis of secondary efficacy objectives

All secondary efficacy analysis will be based on the FAS (observed data only).

2.7.1 Secondary endpoints

The secondary efficacy variables are the following:

- proSPI (s, p, i) score at all assessment periods
- saSPI (s, p, i) score at all assessment periods
- Dermatology life quality index (DLQI) score at all assessment periods
- saPASI score at all assessment periods
- Psoriasis Symptom diary at all assessment periods
- correlation between each of proSPI (s, p, i) and DLQI, and proSPI (p, i) and PASI, at all assessment periods

2.7.2 Statistical hypothesis, model, and method of analysis

ProSPI and saSPI

Descriptive statistics of absolute values and change from Baseline at all assessment periods for proSPI (s, p, i) and saSPI (s, p, i) will be presented separately.

The number and percentage of proSPI (p, i) and saSPI (p, i) will be presented by visit and by the following score bands: 0, 1, 2, …, 9, 10. Graph of reponse distribution of proSPI (p, i) and saSPI (p, i) will be presented by the aforementioned score band at Week 16.

DLQI

The DLQI contains six functional scales (symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. Details on the calculation of DLQI are given in Appendix 5.2.

For each of the seven scores the percentage change from Baseline at each visit will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit.

Number and percentage of patients achieving DLQI status 0 or 1 will be provided by visit.

SaPASI

Absolute value, absolute change and percentage change from Baseline of saPASI score will be summarized by sivit. The number and percentage of saPASI score will be presented by body region, symptom, and visit.

Psoriasis Symptom Diary

Descriptive summary statistics will be presented for absolute values and change from Baseline by visit for intensity of pain, itching and scaling separately.

Correlations between scores

Computation of Spearman's correlation coefficient at each post-Baseline visit and graphing of scatterplot at Week 16 will be performed on the following scores:

- between proSPI (s, p, i) and DLQI (total score)

- between proSPI (p, i) and PASI

2.7.3 Handling of missing values/censoring/discontinuations

Missing values for the secondary variable will not be replaced. Subjects with no post-Baseline value will be excluded from this analysis.

2.8 Safety analyses

Analysis of safety data will be on the SAF.

2.8.1 Adverse events (AEs)

AEs will be presented for the whole study period.

Only AEs that are treatment emergent are summarized. Treatment emergents are defined as events started after the first dose of study medication or events present prior to the first dose of study medication but increased in severity, frequency or clinical feature based on PT and started prior to end of study.

Treatment-emergent adverse events (TEAEs) will be included in all summaries and listings. AEs occurring after signing of informed consent but before first dose of study treatment and those occurring after study completion will be listed only. If any event has an incomplete onset date, this will be handled as described in Appendix 5.1.

AEs will be coded by primary SOC and PT according to the MedDRA version 19.1 or later.

AEs will be summarized by presenting the number and percentage of patients having any AE, having an AE by SOC, and having an AE by PT. Summaries will also be presented for AEs by severity, study treatment related AEs, serious adverse events (SAEs), AE's leading to study drug discontinuation, and AE's leading to death.

Patients who experienced multiple AEs for a PT will be counted once, similarly for patients with multiple AEs per SOC. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a patient reports more than one AE with the same PT, only the greatest severity will be presented for this AE. If a patient reports more than one AE within the same primary SOC, the patient will be counted only once with the highest severity at the SOC level, where applicable.

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on TEAEs with an incidence greater than 5% and on treatment emergent SAEs and SAE suspected to be related to study treatment will be provided by SOC and PT on the SAF.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

A listing of all AEs will be presented. A column indicating if the AE is treatment emergent or not will be shown. Non-treatment emergent AEs will not be summarized; they will only be listed in final analysis.

2.8.1.1 Adverse events of special interest / grouping of AEs

N/A

2.8.2 Deaths

AEs that lead to death are outlined in Section 2.8.1.

2.8.3 Laboratory data

The summary of the data for laboratory evaluations will be presented for both types of laboratory tests (hematology and biochemistry).

Descriptive summary statistics for the absolute values and changes from Baseline at each study visit will be presented. Descriptive summaries will be presented by type and by laboratory test.

For each parameter, shift tables will be produced in order to compare patient Baseline laboratory evaluation with the observed value at each visit. For these shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high at each visit relative to whether or not the Baseline value was normal, low, or high. These summaries will be presented by laboratory test.

The expanded laboratory ranges and the clinically notable abnormalities of key laboratory tests are given in Appendix 9, Section 13.9 of the study protocol version 5.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

N/A in this section (see Section 2.3.3).

ECG collected at screening will be summarized as part of Baseline characteristics (see Section 2.3.3)

2.8.4.2 Vital signs

Vital signs will be presented for the whole study period. Analysis of the vital sign measurements using summary statistics for the absolute values and changes from Baseline at each non-missing post-Baseline visit will be performed. These descriptive summaries will be presented by vital sign parameter.

The number and the percentage of subjects with notable vital signs will be presented. The criteria for notable vital sign abnormalities are provided in Appendix 8, Section 13.8 of the study protocol version 5.

All information collected will be listed by patient and visit. Notable abnormal values will be flagged.

2.9 Pharmacokinetic endpoints

N/A

2.10 PD and PK/PD analyses

N/A

2.11 Biomarkers

N/A

2.12 Other exploratory analyses

Exploratory analyses in this subsection will be on the FAS (observed data only).

Correlations between scores

Correlations between saSPI (s, p, i) and DLQI, proSPI (s, p) and saSPI (s, p), saSPI (s) and PASI, proSPI (s) and saPASI, saSPI (s) and saPASI will be evaluated using the Spearman correlation coefficient. Scatterplots will be presented at Week 16.

Responsiveness to change

An analysis of the SPI responsiveness to change will be led in order to investigate if reductions in psoriasis severity based on PASI scores would be accompanied by corresponding reductions in proSPI (s) and saSPI (s) scores at Week 16. This analysis will be performed by the calculation of receiver operating characteristic (ROC) and area under the curve (AUC). Three criteria of response will be examined to evaluate each score: ≥50%, ≥75%, ≥90%, and 100% reduction in PASI score.

For each binary PASI response (e.g. for PASI75, 1 if ≥75% and 0 otherwise), a logistic regression will be performed where proSPI (s) and saSPI (s) are the independent variables in separate models. The nonparameteric methods described in DeLong et al. (1988) will be used to compute the AUC value and 95% CIs for each curve. From the regression models, odds ratios along with their 95% CIs, and AUC values along with their 95% CIs will be presented.

Sexual dysfunction

To explore sexual dysfunction in the subset of patients willing to complete sexual function questionnaire, descriptive summary statistics will be presented for absolute values and change from Baseline for BISF-m and BISF-w scores at all assessment periods.

Each of the BISF-m and BISF-w index contain seven dimensions (thoughs/desire, arousal, frequency of sexual activity, receptivity/initiation, pleasure/orgasim, relationship satisfaction, problems affecting sexual function). Eight scores will be derived from the answers to the

questionnaires: the score of each of the seven dimensions as well as the composite score computed from all dimensions. Details of the calculation are given in Appendix 5.3.

2.13 Interim analysis

No interim analysis is planned in this study.

3 Sample size calculation

The samples size calculation is based on the primary objective of the study which is to evaluate the benefit of secukinumab on the severity and psychosocial burden of psoriasis based on SPI change at Week 16 compared to Baseline in patients suffering from moderate to severe plaque psoriasis.

A similar study by Chularojanamontri et al. (2013) showed that it is possible to detect responsiveness and a minimum clinically important difference (an absolute change of 5 and 7 for proSPI (s) and saSPI (s), respectively) derived from PASI changes with 100 patients. The study showed a SD of 7.35 and 10.35 in change from Baseline at Week 10 in proSPI (s) and saSPI (s) respectively. As the SD at Week 16 is expected to be higher, conservative SD estimates of 14 and 19 will be assumed for change at Week 16 for proSPI (s) and saSPI (s) respectively.

Based on an analysis of paired differences, in order to have at least 90% power to detect a significant clinical difference for each index at the 2.5% level (2-sided), it can be estimated that a sample size of 100 evaluable patients would be sufficient.

Taking into account an anticipated drop-out of 20 patients, 120 patients will need to be included in the study.

4 Change to protocol specified analyses

Any objectives to be assessed until Week 56 will be changed to until end of study.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

The following table explains the notation used in the logic matrix. Please note that completely missingstartdateswillnotbeimputed.

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

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

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 < investigational study treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = investigational study treatment start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the 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).

c. If the AE start date year value is greater than the investigational study 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).

c. 4. If the AE start date year value is equal to the investigational study treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the treatment reference start date + 1 day.
   b. Else if the AE month is less than the investigational study treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the investigational study 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), treatment start reference date + 1 day).

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

5.1.2 Concomitant medication date imputation

5.1.2.1 CM start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missingstartdateswill notbeimputed.

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

Thefollowingmatrixexplainsthelogicbehindtheimputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

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 investigational study 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 investigational study 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 start date year value is equal to the investigational study 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 to 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.

5.1.2.2 CM end date imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment follow up period date, last day of the month, date of death).
4. If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.2 Calculation of Dermatology Life Quality Index (DLQI)

DLQI contains six functional scales (symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). Each question will be answered with the following response: “not at all”, “a little”, “a lot”, “very much”, or “not relevant”. Seven scores will be derived from the DLQI: the score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

Scoring
The scoring of each question is as follows:

Table	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0
Yes (Question 7: “prevented work or studying”)	3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

Meaning of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

Detailed analysis of the DLQI

The DLQI can be analysed under six headings as follows:

Section	Question	Score
Symptoms and feelings	1, 2	maximum 6
Daily activities	3, 4	maximum 6
Leisure	5, 6	maximum 6
Work and School	7	maximum 3
Personal relationships	8, 9	maximum 6
Treatment	10	maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Interpretation of incorrectly completed questionnaires

There is a very high success rate of accurate completion of the DLQI. However, sometimes subjects do make mistakes.

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered 'yes' this is scored 3. If question 7 is answered 'no' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If "Not relevant" is ticked, the score for Question 7 is 0. If it is answered 'no', but the second half is left incomplete, the score will remain 0.
4. If two or more response options are ticked, the response option with the highest score should be recorded.
5. If there is a response between two tick boxes, the lower of the two score options should be recorded.
6. The DLQI can be analysed by calculating the score for each of its six sub-scales (see above). When using sub-scales, if the answer to one question in a sub-scale is missing, that sub-scale should not be scored.

5.3 Calculation of Brief Index of Sexual Functioning for men and woman (BISF-M and BISF-W)

The calculation of BISF-W will be based on Mazer et al. (2000). A similar method will be adopted for calculation of BISF-M. As per French author recommendations, Dr François Petit (email to the CPO on 09/01/2017), BISF-M and W scoring rules for the French questionnaire need to be adapted in order to keep the same reference ranges.

Each of the BISF-M and BISF-W index consists of seven dimension scores describing seven aspects of sexuality. The dimensions are as follows:

Dimension (name)	Question	Score range
D1 (thoughts/desire)	Q3 + Q4	0 to 12
D2 (arousal)	Q5 + Q6	0 to 12
D3 (frequency of sexual activity)	Q7	0 to 12
D4 (receptivity/initiation)	Q8 + Q9 + Q12	0 to 15
D5 (pleasure/orgasm)	Q10 + Q11	0 to 12
D6 (relationship satisfaction)	Q18 + Q19 + Q20	0 to 12
D7 (problems affecting sexual function)	Q14 + Q15 + Q16 + Q17	0 to 16

Detailed analysis of the answers to questionnaires

Calculation for each of the twenty two questions is as follows.

Q1. yes/no responses are not scored.

Q2. yes/no responses are not scored.

Q3. responses are scored as (0) = 0, (1) = 1, (2) = 2, (3) = 3, (4) = 4, (5) = 5, (6) = 6. The possible score range is 0 to 6.

Q4. responses for each of the seven items are scored as (0) = 0, (1) or (2) = 1, (3) = 3, (4) = 4, (5) = 5, (6) = 6. The final score is the sum of the item scores divided by 7. The possible score range is 0 to 6.

Q5. responses for each of the eight items are scored as (0) = 0/not applicable, (1) = 0, (2) = 1, (3) = 2, (4)= 3, (5) = 4. The final score is the sum of the item scores divided by 4. The possible score range is 0 to 8.

Q6. responses are scored as (0) = 0/not applicable, (1) = 4, (2) = 3, (3) = 2, (4) = 1, (5) = 0. The possible score range is 0 to 4.

Q7. responses for each of the eight items for BISF-W (nine items for BISF-M) are scored as (0) = 0, (1) = 1, (2) = 2, (3) = 3, (4) = 4, (5) = 5, (6) = 6. The final score for BISF_W and BISF_M is the sum of the item scores divided by 4 and 4.5 respectively. The possible score range is 0 to 12.

Q8. responses are scored as (0) = 0/not applicable, (1) = 0, (2) = 6, (3) = 4, (4) = 2. The possible score range is 0 to 6.

Q9. responses are scored as (0) = 0/not applicable, (1)= 0/not applicable, (2) = 0, (3) = 1, (4) = 2, (5) = 3, (6) = 4, (7) = 5. The possible score range is 0 to 5.

Q10. responses are scored as (0) = 0/not applicable, (1) = 0/not applicable, (2) = 0, (3) =1, (4) = 2, (5) = 3, (6) = 4. The possible score range is 0 to 4.

Q11. responses for each of the eight items for BISF-W (nine items for BISF-M) are scored as (0) = 0/not applicable, (1) = 0/not applicable, (2)= 0, (3) = 1, (4) = 2, (5) = 3, (6) = 4. The final score for BISF_W and BISF_M is the sum of the item scores divided by 4 and 4.5 respectively. The possible score range is 0 to 8.

Q12. responses are scored as (0) = 0/not applicable, (1) = 4, (2) = 2, (3) = 0. The possible score range is 0 to 4.

Q13. responses for each of the five items are scored as (0) = 0/not applicable, (1) = -2, (2) = -1, (3) = 0, (4) = 1, (5) = 2. The final score is the sum of the item scores. The possible score range is -10 to 10. This question measures change during the past month and does not contribute to any dimension.

Q14. responses for each of the eight items for BISF-W (seven items for BISF-M) are scored as (0) = 0, (1) = 1, (2) = 2, (3) = 3, (4) = 4. The final score for BISF_W and BISF_M is the sum of the item scores divided by 8 and 7 respectively. The possible score range is 0 to 4.

Q15. responses for each of the five items (including other, if specified) are scored as (0) = 0/not applicable, (1)= 0, (2) = 1, (3) = 2, (4) = 3, (5) = 4. The final score is the sum of the item scores divided by 5. The possible score range is 0 to 4.

Q16. responses are scored at (0) = 0, (1) = 1, (2) = 2, (3) = 3, (4) = 4. The possible score range is 0 to 4.

Q17. responses are scored as (0) = 0/not applicable, (1)= 4, (2) = 3, (3) = 2, (4) = 1, (5) = 0. The possible score range is 0 to 4.

Q18. responses are scored as (0) = 0/not applicable, (1) = 4, (2) = 3, (3) = 2, (4) = 1, (5) = 0. The possible score range is 0 to 4.

Q19. responses are scored as (0) = 0/not applicable, (1) = 4, (2) = 3, (3) = 2, (4) = 1, (5) = 0. The possible score range is 0 to 4.

Q20. responses are scored as (0) = 0, (1) = 1, (2) = 2, (3) = 3, (4) = 4. The possible score range is 0 to 4.

Q21. responses are not scored. This question provides information on sexual orientation not pertinent to the scoring of any dimension.

Q22. responses are not scored. This question provides information on sexual orientation not pertinent to the scoring of any dimension.

Composite score

The composite score will be calculated based on the seven dimension scores as:

$$D1 + D2 + D3 + D4 + D5 + D6 – D7$$

Here, D7 subtracted in the formular so that a higher composite scores represents greater sexual function.

5.4 SAS code

Paired t-test with multiplicity correction

```
/* Perform paired t-test and output p-value on variable DIFF (paired
difference of two variables of interest). Repeat for other differences */
proc ttest data=<dataset> sides=2 alpha=0.05 H0=0;
   var DIFF;
```

```
   ods output ttests=ttest_pvalue;
run;

/* Sort all p-values in ascending order */
proc sort data=ttest_pvalue out= allpvaluessorted;
   by probt;
run;

/* Do multiple adjustment on the sorted p-values using Hochberg procedure */
proc multtest pdata(probt)=allpvaluessorted hoc;
run;
```

Receiver Operating Characteristic curve and area under the curve

```
/* The plots=<dataset>(id=prob) specification will display a ROC curve that
will have certain points labeled with their predicted probabilities */
ods graphics on;
   proc logistic data=<dataset> plots=<dataset>(id=prob);
      model <response>(event='1') = <predictor>;
      roc '<predictor's label>' <predictor>;
   run;
ods graphics off;
```

6 Reference

Chularojanamontri L., Griffiths, C.E.M. and Chalmers J.G. (2013). ‘‘The Simplified Psoriasis Index (SPI): A Practical Tool for Assessing Psoriasis’’. *Journal of Investigative Dermatology*, 133, 1956-1962

DeLong, E. R., DeLong, D. M., and Clarke-Pearson, D. L. (1988). “Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach”. *Biometrics*, 44, 837-845

Mazer, N. A., Leiblum, S. R., & Rosen, R. C. (2000). ‘‘The brief index of sexual functioning for women (BISF-W): a new scoring algorithm and comparison of normative and surgically menopausal populations”. *Menopause*, *7*(5), 350-363