NOVARTIS

Clinical Development

AIN457A

CAIN457AIT01 / NCT02394561

A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME) – amended with an extension treatment period of up to 48 weeks

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09-Jun-2016	Prior to DB lock	1st draft version		
04-Jul-2016			Updated as per comments	
04-Aug-2016			Updated as per comments	
17-Sep-2016				
24-Oct-2016		Final version		
16-Jan-2017		Amendment 1.0	Visit Window approach added. DLQI and HADS scoring method added.	Section 2
27-Apr-2017			Added MMRM analysis with MI approach Added Non-responder analysis	

20-Sep-2017	Amendment 2.0	Summaries and analyses are extended based on 72 weeks duration.	General:
		Analysis Sets added for clarity or additional analyses: • All patients: all patients who signed informed consent and entered in the study, including screen failure. • Core phase completers set: All patients who completed the Core phase visits (Week 24) are called core phase completer set.	Section 2.2 Analysis sets
		Analysis Sets updated/ clarified (in bold): • Safety: all enrolled patients included in the FAS population who were given at least one dose of study drug. • Intent-to-treat (ITT): all patients included in the safety population with at least one post-baseline efficacy assessment and with the Cw6 assessement.	Section 2.3.1:
		By visit disposition summary table is added.	
		P-values of comparison of cohorts will be analysed based on stratified CMH, and logistic model with covariates (for categorical variables) and ANCOVA (for continuous variables).	Section 2.3.2:
		Total number of comorbidities (all medical histories) between cohorts will be analyzed by Poisson model adjusted by covariates	Section 2.4.2:
		Previous psoriasis therapies will be analysed by logistic model and total number of such therapies will be analysed by Poisson model after adjusting for covariates.	

	The model factors are clarified in the SAP.	Section 2.5:
	Non-responder imputation is added. Analsyses based on NRI for primary and secondary efficacy endpoints are added.	
	Modelling approaches of PASI scores and IGA scores have been included based on MMRM. Modelling of IGA0/1 responder is also added.	
	The AEs comparison of cohorts will be done based on CI and pvalues generated from logistic model or poisson model (for total number of events overall).	Section 2.8.1
	The AESI of RMP related events will be summarized and compared based on logistic model approach.	Section 2.8.4
	ANCOVA model for vital signs are added.	
	Other minor updates done as per consistency	General

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study report
DAR	Dose Administration Record
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
hs-CRP	High Sensitivity C Reactive Protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IL	Interleukin
ITT	Intent-to-treat
LDH	Lactate Dehydrogenase
LFT	Liver Function test
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PASI	Psoriasis Area Severity Index
PP	Per-Protocol
PPD	Purified Protein Derivative
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes

PUVA	Psoralen combined with Ultraviolet A
QoL	Quality of Life
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SUSAR	Suspected Unexpected Adverse Reaction
TNF	Tumor Necrosis Factor
TFLs	Tables, Figures, Listings
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This document contains details of the statistical methods which will be used in the phase IIIb clinical trial CAIN457AIT01. This document gives detailed statistical methodology used in the analysis of this study. This is a multicenter, prospective study involving Cw6-negative and Cw6-positive patients affected by moderate to severe chronic plaque psoriasis.

The study has four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks and an extension period of 48 weeks.

This SAP will be used for the analysis of both Core phase and Extension phase.

Data will be analyzed by statistical software SAS version 9.2 or later according to the data analysis Section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Study design

This is a multicenter, prospective study involving Cw6-negative and Cw6-positive patients affected by moderate to severe chronic plaque psoriasis.

The study has four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks and an extension period of 48 weeks. The schematic of study design is given in Figure 1.1-1 (for Core phase) and in Figure 1.1-2 (for Extension phase) below.

At pre-screening (day -28), patients will be centrally assessed for Cw6 positivity or negativity and stratified into two cohorts (Cw6-negative and Cw6-positive patients). Both patients and investigators will be blinded to the results with respect to Cw6. At the same time 308-TNF α polymorphism will be centrally determined.

After a full screening visit, each eligible patient will be treated according to an induction regimen of two injections of secukinumab 150 mg a week for five weeks starting at baseline (week 0), followed by a maintenance period of one treatment (two injections) per month. At week 16, patients achieving a PASI 50 response will be eligible to continue on secukinumab for an additional 8 weeks. After a total of 24 weeks, willing patients reaching at least a PASI 75 response will enter an extension treatment period of up to 48 weeks.The total duration of the study, including the extension period, is therefore of 72 weeks. For all summaries of “by phases” analyses, total number of patients (N) for extension phase will be the number of patients who have entered the extension. All percentages in extension phase will be based on this N.

Primary analysis time point

The primary analysis will be performed at 16 weeks , and thereafter for up to 72 weeks.

Planned number of patients

The study plans to enroll about 406 adult men or women, of which 365 are evaluable patients, diagnosed with moderate to severe chronic plaque psoriasis for at least 6 months. The patients must be candidates for systemic therapy and may be treatment naïve or have failed to respond to other systemic therapy (including cyclosporine, methotrexate, psoralen combined with ultraviolet A (PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these).The study plans to involve approximately 50 centers. The extension phase will include approximately 306 of the patients initially enrolled in the core study.

Interim analyses

No interim analysis will be performed for this study.

Figure 1.1-1: Study Design for Core Phase

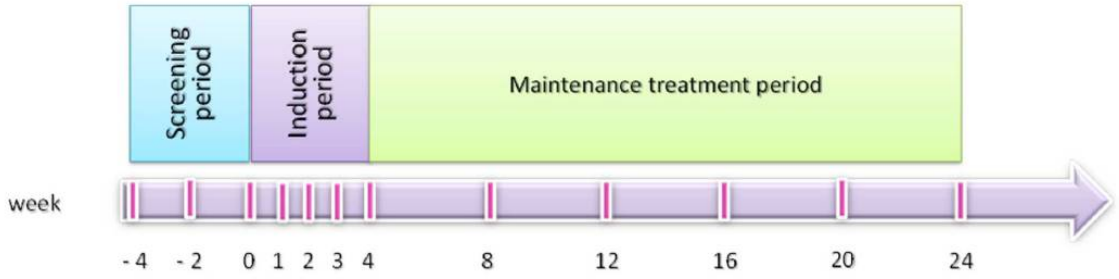
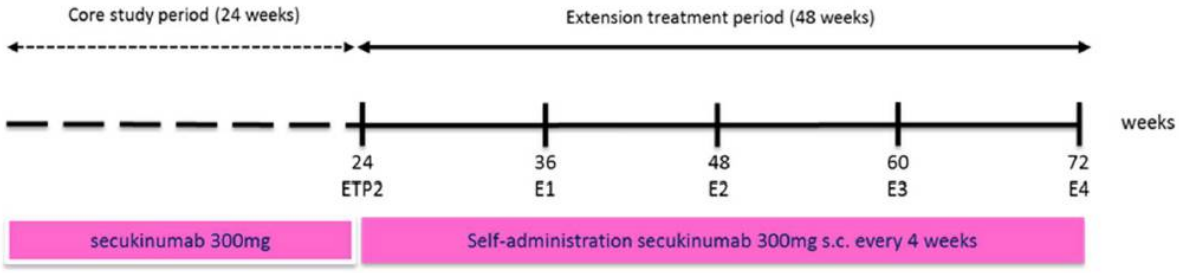


Figure 1.1-2: Study Design for Extension Phase



1.2 Study objectives and endpoints

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	
To evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and	PASI 90 response after 16 weeks of treatment, defined as the achievement of ≥ 90% improvement (reduction) in PASI score after 16 weeks of treatment compared to baseline, and thereafter for

thereafter for up to 72 weeks.	up to 72 weeks.
Secondary objective	
To compare the proportion of responders to PASI 50/75/90/100 between cohorts at each time point.	Proportion of responders to PASI 50/75/90/100 at each time point.
To compare the mean changes vs baseline in the Investigator's Global assessment (IGA) mod 2011 between cohorts at each time point.	Change from baseline in IGA mod 2011 between Cw6-negative and Cw6-positive at each time point.
To compare time to reach PASI 90 between cohorts.	Time to PASI 90 response between Cw6-negative and Cw6-positive.
To compare time to reach PASI 75 between cohorts.	Time to PASI 75 response between Cw6-negative and Cw6-positive.
To evaluate the quality of life by means of the Dermatology Life Quality Index (DLQI) in all patients at each time point.	Change from baseline in DLQI at each time point.
To evaluate anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) in all patients at each time point.	Change from baseline in HADS at each time point.
To evaluate the correlation between HADS and PASI in all patients.	Correlation coefficient between HADS and PASI.
To evaluate changes from baseline in weight, BMI and waist in all patients at each time point.	Change from baseline in weight, BMI and waist at each time point.
To compare safety and tolerability between cohorts during the 24 weeks, and then during the whole study period.	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory, vital signs , ECG values and chest X-ray from values baseline.
To evaluate the amount of resources used during the study in comparison with the 6 months prior to the beginning of the study.	Health resources use will be conducted considering the comorbidities (such as anxiety and depression), PsO medical history, concomitant medication and adverse event.
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis. Health economics input analyisis will be provided by [redacted]. It is planned that the data from all centers that participate in this protocol will be used for analysis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

The data from all centers will be pooled and summarized. Continuous data will be summarized by n, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %). Unless stated otherwise, two-sided p-values will be presented.

Decimal places

Decimal places will be as follows:

- p-value: 4 decimal places; if p-value is less than 0.0001, display <0.0001.
- standard error and standard deviation: data precision + 2 decimal places
- mean, quartile, percentile and median: data precision + 1 decimal place
- minimum and maximum: same as data precision
- percentages: 1 decimal place, 0% will be displayed as 0.0 and 100% will be displayed as 100.0.
- Odds ratios, risk ratios and hazard ratios will be displayed with 3 decimal places.
- Confidence interval (CI): data precision + 2 decimal place.

P-values will not be concatenated with "*" stars in case of significance.

2.1.1 General definitions

2.1.1.1 Study treatment: Study treatment refers to:

Secukinumab 300 mg (two s.c. injections of secukinumab 150 mg).

2.1.1.2 Study treatment start and end date:

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Dose Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page.

2.1.1.3 Study day:

Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g.visit, lab samples, AEs). For events prior to study drug start date (e.g., an adverse event occurred before the start of first dose), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

Due to the study drug dosing schedule, one month will be considered as 28 days. Time from events prior to the start of study drug, e.g., time since diagnosis, is calculated as the difference between the start date of study drug and the date of prior event.

Note that, the first dose day is Day 1, and the day before the first dose day is counted as Day -1 (not Day 0).

2.1.1.4 Baseline and post baseline:

In general, a *baseline* value refers to measurement corresponding to week 0 assessment. A post-baseline value refers to a measurement taken after week 0 assessment.

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

For DLQI, In case baseline value is zero (0), percentage change will be calculated as (post-baseline value -0)*100 %.

2.1.1.5 Study periods:

The study has four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks and an extension period of 48 weeks.

For analyses which will be done by phases (i.e., Core and Extension separately) the following rules will be applied to summarize the data.

For spontaneous data (CM, AE) as below:

- For the subjects who did not enter Extension Phase, all events/medications belongs to Core Phase

- If event/medications start date is on or before visit date of E0, then APERIOD=Core Phase
- If event/medications start date is after visit date of E0, then APERIOD=Extension Phase.

For Planned data (i.e., Visit wise, all safety and efficacy) will be derived as below:

- Visits before E0 will belong to Core Phase
- Visits on or after E0 will belong to Extension Phase

Basically reporting will be done for visit assessment data in extension phase which is collected on or after ICF is signed for extension phase.

The above rules are irrespective of whether V12 visit date and E0 visit date are same or different.

2.1.1.6 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 the below Table 2.1, 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 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 patient is delayed and occurs on Day 46 instead of on Day 28, 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.

Table 2.1 Assessment windows for scheduled visits

Visit	Week	Scheduled day	Visit Window
Screening (Visit1, Visit2)	-4	-28	-28 Days to Day -4
Baseline (Visit 3)	0	1	-3 day to Day 1
Visit 4	1	7	Day 2-10
Visit 5	2	14	Day 11-17
Visit 6	3	21	Day 18-24
Visit 7	4	28	Day 25-42
Visit 8	8	56	Day 43-70
Visit 9	12	84	Day 71-98
Visit 10	16	112	Day 99-126
Visit 11	20	140	Day 127-154
Visit 12	24	168	Day 155-210
E1	36	252	Day 211-294
E2	48	336	Day 295-378
E3	60	420	Day 379-462
E4	72	504	≥ 463 Day

Case 1) If V12 and E0 visit dates are same then:

Visit	Wk	Day	Window
V12	24	168	Day 155-210
E1	36	252	Day 211-294
E2	48	336	Day 295-378
E3	60	420	Day 379-462
E4	72	504	≥ 463 Day

Case 2) If V12 and E0 dates are different then:

Visit	Wk	Day	Window
V12	24	168	Day 155-(A(E0)-1)
E0	24	A(E0)	A(E0) – (A(E0) +42)
E1	36	(A(E0) +43)+41	Day (A(E0) +43) – (A(E0) +43+83)
E2	48	(A(E0) +43+84)+41	Day (A(E0) +43+84) – (A(E0) +43+2*83)
E3	60	(A(E0) +43+2*83+1)+41	Day (A(E0) +43+2*83+1) – (A(E0) +43+3*83)
E4	72	(A(E0) +43+3*83+1)+41	> Day (A(E0) +43+3*83)

Where A(E0) date implies Actual Visit date of E0.

Note if A(E0) date = Day 168, which is the theoretical study day of V12, then both the table gives same windows.

If E0 is not assessed, then combine the window of E0 and E1 for E1 visit, i.e., E1 window will start from E0. Target day of E1 will remain same.

For parameters which are not collected at every visit (e.g. DLQI, HADS, [redacted]), visit windows defined in Table 2.1 will be combined. For example, if a parameter is measured at Week 16 and Week 24 only, Week 16 visit window will extend from Day 2 to Day 126 (combining Week 1 to Week 16 visit windows), Week 24 will extend from Day 127 to Day 210 (combining Week 20 to Week 24 visit windows). Similarly, in extension phase, if a parameter is measured at E2 and E4 only, E2 window will extend from E0 to (A(E0) +43+2*83) (combining E0 to E2 visit windows) and E4 window will extend to > (A(E0) +43+2*83) (combining E3 to E4 visit windows).

For any assessments which are only in Core phase, and if any results are mapped to extension phase analyses visits, then such records will not be displayed at extension.

If more than one assessment falls into the interval, the rules defined in Section 2.1.1.7 below are applied.

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

2.1.1.7 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 (SeeTable 2-2).

For baseline assessment definition see in Section 2.1.1.4. 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.

Table 2-2 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See section 2.1.1.4
Post-baseline efficacy	All data except DLQI, HADS	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.
Post-baseline efficacy	DLQI,HADS	The measurement closest to the target day will be used. In the event two measurements are taken equally apart, the earlier one will be used. If two measurements have been taken on the same day, select the worst.
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 measurments 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).

2.2 Analysis sets

The following analysis populations will be defined for statistical analysis.

- All patients: all patients who signed informed consent and entered in the study, including screen failure.
- Full Analysis Set (FAS): all enrolled patients (i.e. patients entered at week 0 – visit 3).
- Safety: all enrolled patients included in the FAS population who were given at least one dose of study drug.
- Intent-to-treat (ITT): all patients included in the safety population with at least one post-baseline efficacy assessment and with the Cw6 assessement.
- Per-Protocol (PP): all patients included in the ITT population who completed the study without any major protocol violation.
- Core phase completers set: All patients who completed the Core phase visits (Week 24) are called core phase completer set.

The primary and secondary objectives will be evaluated on the ITT population. A supportive analysis will be done on the PP population.

All safety evaluations will be based on the safety set.

2.2.1 Subgroup of interest

There is no planned subgroup of interest.

2.3 Patient disposition, demographics and other baseline characteristics

All data about patient demographics and baseline characteristics, including derived variables, will be summarized by cohort and overall with summary descriptive statistics on the Safety set. Continuous data will be summarized by n, mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %). P-values will also be displayed for both categorical and continuous variables, wherever required.

The number of patients in each analysis populations will be described and the reasons for excluding a patient from any particular population will be provided with the number of protocol violators for each criterion. The difference between cohorts with respect to protocol deviations and reasons for dropout will be examined by summarizing the protocol deviations by cohorts and overall on the all patients. Also, Major protocol deviations by cohorts and overall on the all patients will be summarized.

Major protocol deviations are the deviations with Protocol Deviation IDs (DVSPID) as INCL01, INCL02, INCL03, INCL04, INCL05, EXCL02, EXCL03, EXCL04, EXCL05, EXCL06, EXCL07, EXCL15, EXCL16, EXCL19, COMD01, COMD02, COMD03, COMD04, COMD05, COMD06, COMD07, COMD08, COMD09, COMD11, COMD14, COMD16, COMD17, COMD18 , COMD19, OTH08 and also patient's meeting the below criteria

- No secukinumab administration

- No valid PASI assessment after baseline
- Patient who didn't complete the study
- Patient's without Cw6 assessment.

Note:
- Prior use of prohibited PsO medication without the recommended wash-out period (PD: COMD01, COMD03, COMD05, COMD07, COMD09, COMD11, COMD16, COMD17, COMD18 , COMD19).
- Concomitant use of PsO medication (PD: COMD02, COMD04, COMD06, COMD08, COMD10, COMD12, COMD14, COMD17, COMD18 , COMD19).

2.3.1 Patient disposition

Summary of disposition for screening phase and study completion phase will be presented separately on All patients data.

For screening phase disposition, the number and percentage of patients screened, screen completed and discontinued will be summarized by cohorts and overall with reasons for discontinuation on All patients.

For patient's disposition, the number and percentage of patients screened, enrolled, completed and discontinued will be summarized by cohorts and overall in each study phase (i.e. Core and extension) with reasons for discontinuation on All patients.

Patient number and whether they completed or discontinued from the study at screening phase disposition and study completion core/extension phase disposition will be listed separately,with date of discontinuation and primary reason for discontinuation as applicable.

A brief summary of patients entered at each study visit will be provided.

2.3.2 Patient demographic and other baseline characteristics

Summary statistics n, mean, median, standard deviation, minimum, maximum, first and third quartiles will be presented for continuous variables for each cohort and overall on the Safety set. The number and percentage of patients in each category will be presented for categorical variables for each cohort and overall on the Safety set.

The following demographic and baseline variables will be summarized:

Demographic variables:

Continuous variables:

- Age (years)
- Height (cm)
- Weight (kg)
- Waist (cm)
- BMI (kg/m^2) will be calculate as (body weight in kilograms) / $(\text{height in meters})^2$

Categorical variables:

- Age categories (<65, >=65)
- Sex (Male, Female)
- BMI categories (<25 vs >=25)
- Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
- Ethnicity (Hispanic or Latino, Chinese, Japanese, Indian, Mixed Ethnicity, Other)
- Geographical region (north vs south/central)
- Smoking status at baseline
    - Never
    - Current
    - Former

Baseline disease characteristics variables:

Continuous variables:

- Baseline PASI score
- Baseline IGA mod 2011 score
- Age at diagnosis of psoriasis (years)
- Time since first diagnosis of psoriasis (years)
  (which is derived as date of baseline visit-date of first diagnosis of psoriasis)
- Time since first diagnosis of psoriatic arthritis (years)
  (which is derived as date of baseline visit-date of first diagnosis of psoriatic arthritis)

Categorical variables:

- Type of psoriasis history at diagnosis
    - Plaque type psoriasis
    - Nail psoriasis
    - Scalp psoriasis
- Number of patients with psoriatic arthritis
- Type of psoriatic arthritis
    - Polyarticular
    - Monoarticular
    - Axial
    - Enthesitis
    - Dactylitis
- Quantiferon TB-Gold test
    - Negative
    - Positive
    - Indeterminate
- PPD test
    - Negative

  - Positive
  - Indeterminate
- TNFα - 308 polymorphism
  - Heterozygous
  - Homozygous
- Metabolic syndrome
  - Yes
  - No

Definition of metabolic syndrome
Metabolic syndrome is defined as the presence of at least 3 of the 5 following criteria(Expert Panel JAMA 2001) :

- Increased waist circumference (≥102 cm for men, ≥ 88 cm for women).
- elevated triglycerides (≥150 mg/dl).
- Reduced high-density lipoprotein (HDL) cholesterol (≤ 40 mg/dl in men and ≤ 50 mg/dl in women).
- Elevated blood pressure (≥ 130 mmHg systolic and ≥ 85 mmHg diastolic or ongoing treatment for hypertension).
- Elevated glucose (≥100 mg/dl or ongoing treatment for elevated glucose)

In order to interpret results adequately, the homogeneity of patient distribution between cohorts will be tested on selected baseline demographics and anamnestic variables (e.g. for gender, age, race, ethnicity, BMI, baseline PASI, baseline IGA, TNFα - 308 polymorphism, metabolic syndrome, smoking).

Categorical variables – as race, ethnicity, geographical region and type of PsA will be analyzed by Cochran-Mantel-Haenszel, while the remaining variables listed in the table below will be analyzed by means of a regression logistic model.

Continuous variables will be analyzed by means of an ANCOVA model corrected as indicated in the table below.

Number of patients with presence of PsA will be analyzed by means of Chi Square test.

Moreover, differences between cohorts in BMI, height, weight, waist, geographical distribution, type of psoriasis, age at PsO diagnosis, time since PsO diagnosis, concomitant PsA, type of PsA, time since PsA diagnosis, quantiferon TB-Gold, PPD test will be also explored. Variables reported in the table below will be included as covariates in the explanatory analysis model.

Normality data distribution will be assessed by means of Shapiro-Wilk test and with graphical methods (if possible). In case of non-normality, a non-parametric test will be used, if feasible.

Variable analyzed	**Covariates/stratification factors**
Age/ age group	Sex

Sex	Age
BMI/height/weight/waist/ BMI categories	Age, sex
Type of PsO (other than plaque)/ Time since PsO diagnosis/ age at PsO diagnosis/ presence of PsA/ time since PsA diagnosis/ metabolic syndrome	Age, sex, waist
PASI at baseline / IGA at baseline	Age, sex, waist, type of PsO, time since PsO diagnosis, presence of PsA
Race/ethnicity/geographical region/ Type of PsA	none
Smoking status	Age, sex
TNF-alpha polimorphism / quantiferon / PPD	Age

Medical history

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary version 18.1 or latest available. They will be summarized by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary on the Safety set and will be presented by cohorts and overall.

Differences in total number of comorbidities (i.e., all medical histories with categories General) between cohorts will be assessed by means of a Poisson model taking into account the following factors: age (tertiles), sex and time since PsO diagnosis. In this case, the total number of medical histories are to be considered for all patients by cohort. Additionally Poisson analyses will be done for total number of comorbidities including PsA category along with General category of MH will also be performed.

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

2.4.1 Study treatment / compliance

Summary of treatment exposure and compliance by cohort and overall will be presented up to week 24 for Core phase analysis, from E0 to E4 for extension phase and overall from visit 3 to E4 on the Safety set.

Duration of exposure

The exposure to investigational drug (number of doses) and duration of exposure (days) will be summarized by cohort and overall.
Duration of exposure will be defined as the time from first dose of study treatment to the last dose of study treatment for all patients.

Compliance

Compliance will be calculated based on documented study treatment administration details and displayed by cohort and overall as well as study period (i.e. induction, maintenance and

extension). Total actual dose will be compared with the total dose patients should take as per protocol and derived compliance will be summarized.

Total actual dose for Core phase will be derived as

Total actual dose = Actual amount of dose of Secukinumab 300 mg upto week 24 × Frequency of dose upto week 24.

The treatment compliance will be calculated as

$$\text{Treatment compliance (\%)} = \frac{\text{the actual number of injections received by a patient}}{\text{the scheduled number of injections}} \times 100.$$

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons.

Similar definition will also hold for extension and overall duration.

Drug interruptions

The number and percentage of patients with study drug interruptions and the reasons that led to the interruption will be summarized by cohort and overall as well as per study period (i.e. induction, maintenance and extension) on the Safety set.

2.4.2 Prior, concomitant and post therapies

The use of rescue medication, concomitant medications and significant non-drug therapies will be summarized by Anatomic Therapeutic Chemical (ATC) class – level 2 and PT, by cohort and overall on the Safety set.

Prior and concomitant therapies

Any medications entered will be coded using the WHODrl dictionary version WHODD 1 or latest available. Concomitant medications will be summarized in separate tables by cohorts and overall on the Safety set. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes level 2 and PT, grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Previous psoriasis therapies will also be summarized by cohort including p-values which will be calculated using logistic regression, adjusted by age (tertiles), sex and number of comorbidities.

Additionally, the number of patients naive, number of patients with previous systemic therapy, and number of patients with previous biologic therapy will also be summarized. The categories “Topical”, “Phototherapy”, “Missing” will NOT be counted to derive the Naïve group.

Moreover the total number of previous psoriasis therapies will be analyzed similar to total number of comorbidities (General and PsA) and p-values (using same model and covariates) will be reported for comparison of cohorts.

Concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date.

Rescue medication

Rescue medication is defined as medication used to control symptoms that are not adequately controlled on study treatment.

The treatments 'METILPREDNISOLONE', 'ACITRETINE', 'ELOCON CREAM' with reasons in 'WORSENING OF PSORIASIS', 'ERYTHEMA AND DESQUAMATION IN PSORIASIS AREA', 'ERYTHEMATOUS DESQUAMATIVE LESIONS ON THE PALMS OF HANDS' will be considered as rescue medication for this study.

Rescue medication will be summarized by Anatomic Therapeutic Chemical (ATC) class and PT, by study phase and by cohort and overall on the Safety set.

Procedures and significant non-drug therapies

Procedures and significant non-drug therapies will be summarized by system organ class (SOC) and preferred term (PT), by cohort and overall on the Safety set.

2.5 Analysis of the primary objective

The primary objective of this study is to evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks.

2.5.1 Primary endpoint

The primary efficacy endpoint is proportion of patients with PASI 90 response after 16 weeks of treatment, defined as the achievement of ≥ 90% improvement (reduction) in PASI score after 16 weeks of treatment compared to baseline, and thereafter for up to 72 weeks.

The primary analysis will be based on the ITT population.

2.5.2 Statistical hypothesis, model, and method of analysis

The proportion of patients who reach PASI 90 at 16 weeks will be presented with the one-tailed 97.5% confidence interval of the Cw6 positive (POS) – Cw6 negative (NEG) difference.

The null hypothesis:

H0: Cw6 POS - Cw6 NEG ≥ 0.12: The difference in proportion of patients achieving PASI 90 response between the Cw6-positive cohort (Cw6 POS) and the Cw6-negative cohort (Cw6 NEG) is at least 12%.

The alternative hypothesis:

HA: Cw6 POS - Cw6 NEG < 0.12: The difference in the proportion of patients achieving PASI 90 response between the Cw6-positive cohort (Cw6 POS) and the Cw6-negative cohort (Cw6 NEG) is less than 12%.

The proportion of PASI 90 response by cohort as well as the difference between cohort together with 97.5% upper CI will be provided using Clopper Pearson CI method.

A logistic regression analysis model will also be fitted, considering age, geographical region (i.e. north vs south vs central), BMI categories (<25 vs >=25), waist circumference, smoking status (Yes vs No), metabolic syndrome (yes vs no), previous PsO therapy (naïve vs previous systemic therapy vs previous biologic therapy), PsA (yes vs no), age at diagnosis of psoriasis, TNFα-308 polymorphism, IGA mod 2011 (severe, moderate, mild) as strata factors.

Model selection:

If model does not converge due to particular covariate(/s), the corresponding covariate(/s) will be removed from the model using Stepwise selection method until model get converged.

Interpretation:

We can conclude that PASI 90 response in the Cw6-negative cohort is not less than 12% with respect to the Cw6-positive cohort if the upper bound of the 97.5 % CI of the difference (Cw6 POS - Cw6 NEG) is less than the non-inferiority margin of 12%.

2.5.3 Handling of missing values/censoring/discontinuations

For patients who prematurely discontinue the study for any reason or patients with missing visits (after baseline), PASI will be imputed using the Last Observation Carried Forward (LOCF) approach. Additionaly non-responder imputation (NRI) analysis will be performed on primary endpoint (i.e., PASI 90 response with logistic regression analysis).

Non-responder imputation rule:

Non-responder imputation will be used: Missing values with respect to response variables based on PASI score will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues), exceptions will apply to the following:

• If a subject dropped out the study prior to last scheduled visit and being responders consecutively at least for two preceding visits, the subject will be imputed as responder for the last scheduled visit.

• If a subject who was responder at visit x-1 and visit x+1 but has missing data at visit x, then the subject will be imputed for visit x.

The approach describes above will be adopted also for PASI 90 assessement reported in the extension phase.

The LOCF approach, as well as the NRI approach will be performed for drop-outs and patients with missing visits in between, however no imputation will be done on any visits for patients – entered in the extension phase **and** who have completed the study before reaching 72 weeks.

2.5.4 Supportive analyses

A sensitivity analysis on the primary efficacy variable will be performed considering the patients who prematurely discontinued the study without a 16-week PASI assessment as non-responders. Hence, for this analysis non-responders patients are those who are PASI 90 responders who prematurely discontinued the study without a 16-week PASI assessment.

Summary of the number and percentage (n and %) of responders patients at week 16 will be presented by cohorts for this supportive analysis. Clopper Pearson confidence interval for a proportion will also be provided.

This supportive analysis will be done on the ITT set.

A supportive analysis on the primary efficacy variable will be also provided using prevalence approach (observed data) on ITT set and also using the PP set using both LOCF and NRI imputation method as well as prevalence approach.

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1.2-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

The analyses of all secondary efficacy endpoints will be based on the ITT.

Refer to Table 1.2-1 of Section 1 for the list of secondary endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

PASI

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 response by visit will be presented with absolute and relative frequencies. Confidence intervals for response rates will be derived as well, based on the score method including continuity correction (Newcombe 1998). The summaries will be done using prevalence (observed data), LOCF and NRI approaches.

Summary statistics will be provided for absolute PASI scores and for percent changes from baseline by visit and cohort using prevalence, and LOCF approches. Graphical representations will also be provided on ITT set.

The two cohorts will be compared on PASI scores (absolute change from baseline) using MRMM model with LOCF, prevalence and MI approaches on ITT set.

PASI Changes vs baseline: Linear Mixed Model for Repeated Mesurements (MMRM):

In order to evaluate if there is a differences between cohorts in PASI changes at each time point vs week 0, a longitudinal analyses of changes from baseline will be performed over the course of the study including all the measurements assessed at each time point for the ITT population using a linear mixed model for repeated measurements (MMRM). An unstructured

covariance matrix for the repeated measures within each patient will be applied in the analysis, if the model does not converge, compound symmetry will be used. The explanatory variables in the longitudinal model include cohort, visit, cohort-by-visit interaction, missing data pattern (completers, missing one assessments, missing two assessments, missing three assessments, etc till all visits in the overall study period), propensity score, and corresponding baseline (week 0). The two cohorts will be compared at each time point by reporting a point estimate, p-value, and 95% confidence interval for the treatment difference, based on least squares means.

The propensity score analysis will consider the following baseline factors: age, geographical region (i.e. north vs south vs central), BMI categories (<25 vs >=25), waist circumference, smoking status (Yes vs No), metabolic syndrome (yes vs no), previous PsO therapy (naïve vs previous systemic therapy vs previous biologic therapy), PsA (yes vs no), age at diagnosis of psoriasis, IGA mod 2011 (severe, moderate, mild) as strata factors. This approach allows us also to maximize the analysis model adding only one variable instead of several ones.

The choice of the MMRM model instead of a simple ANCOVA model on changes vs week 0 considering the prevalence approach or Last observation carried forward (LOCF) approach was done because the LOCF approach would underestimate the within-group mean changes between treatments compared with MMRM, whereas the prevalence approach tend to overestimate the within-group changes (Prakash et al. 2008).

In addition to that, similar MMRM model will be fitted on LOCF and prevalence set without the propensity score approach. An unstructured covariance matrix for the repeated measures within each patient will be applied in the analysis, if the model does not converge, compound symmetry will be used. The explanatory variables in the longitudinal model include cohort, visit, cohort-by-visit interaction, age, geographical region (i.e. north vs south vs central), BMI categories (<25 vs >=25), waist circumference, smoking status, metabolic syndrome (yes vs no), age at diagnosis of psoriasis, and along with interaction terms of each factor with visit.

The SAS codes are described in appendix section.

MMRM with MI approach

MMRM analysis will be also performed using multiple imputation (MI) approach on ITT population.

The multiple imputation will be done with pattern-mixture models (PMMs) as above, that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner.

The SAS codes are described in appendix section.

PASI 75

A logistic regression analysis model will be also fitted, considering age, geographical region, BMI, smoking status, metabolic syndrome, TNF α -308 polymorphism (if feasible), as well as all clinical relevant variable resulting statistically different at baseline between cohort, as strata factors. The analyses will be done similar to primary analyses based on prevalence, LOCF and NRI approaches using ITT set.

Time to reach PASI 90

The differences between cohorts Cw6-negative and Cw6-positive in time to reach PASI 90 will be evaluated by means of a log-rank test. The hazard ratios and their corresponding 95% confidence intervals will be also computed using a stratified Cox proportional hazards regression model with Cw6 group and baseline PASI as explanatory variable and stratified by geographical region and BMI categories, as well as age categories (tertiles).

The Kaplan-Meier estimates of the cumulative rate for each cohort will be plotted, together with p-value. Median time to reach PASI will be also be provided.

Time to reach PASI 75

The differences between cohorts Cw6-negative and Cw6-positive in time to reach PASI 75 will be evaluated by means of a log-rank test. The hazard ratios and their corresponding 95% confidence intervals will be also computed using a stratified Cox proportional hazards regression model with Cw6 group and baseline PASI as explanatory variable and stratified by geographical region and BMI categories, as well as age categories (tertiles).

The Kaplan-Meier estimates of the cumulative rate for each cohort will be plotted, together with p-value. Median time to reach PASI will be also provided.

IGA mod 2011

Summary statistics for the IGA mod 2011 score over time, as well as percent change from baseline, will be presented by visit and cohort.

Changes from baseline between cohorts will be compared using linear mixed model for repeated measurements (with the same covariates used in MMRM model on PASI) on LOCF and prevalence approach.

Summary statistics for IGA 0 or 1 response by visit and cohort will be presented with absolute and relative frequencies. Differences between cohorts at each time point will be explored by means of a logistic regression model adjusting considering age, geographical region (i.e. north vs south vs central), BMI categories (<25 vs >=25), weight, waist circumference, smoking status (Yes vs No), metabolic syndrome (yes vs no), previous PsO therapy (naïve vs previous systemic therapy vs previous biologic therapy), PsA (yes vs no), age at diagnosis of psoriasis, TNFα-308 polymorphism, IGA mod 2011 (severe, moderate, mild) as strata factors for LOCF, NRI and prevalence approach. Similar model selection techniques will be used.

Patient is considered as IGA 0 or 1 responder if the patient achieves a score of 0 or 1 and improved by at least 2 points on the IGA scale compared to baseline.

Dermatology Life Quality Index

Please refer to section 2.11

Hospital Anxiety and Depression Scale

Please refer to section 2.11

2.7.3 Handling of missing values/censoring/discontinuations

For patients who prematurely discontinue the study for any reason or patients with missing visits (after baseline), PASI will be imputed using the Last Observation Carried Forward

(LOCF) approach. If all PASI post-baseline efficacy values are missing, then these missing values will not be imputed and this patient will be removed from the analysis.

A multiple imputation approach on continuous PASI will be also taken into account. If all PASI post-baseline efficacy values are missing, then these missing values will not be imputed and this patient will be removed from the analysis.

2.8 Safety analyses

All the safety analysis will be performed on Safety set by study phase (i.e. CORE and Extensions) and overall.

2.8.1 Adverse events (AEs)

A summary table of AEs will be produced by cohort specifying the number of total events and the absolute and relative frequency of patients with AEs. All AEs which occur on or after the first dose of study treatment and on or before last dose of treatment will be considered as treatment emergent and remaining will be considered as non-treatment emergent. AEs which occur till last visit date of E0 will be reported under Core phase and which start after E0 visit will be reported under Extension phase. The detailed treatment emergent rules for AE reporting by phases are mentioned below:

Core phase

AEs occurring on or after first dose date and

a) on or before the last visit date till E0, if patient discontinued the study

b) on or before the last dose date till E0, if patient completed the study

Extension phase

1) Patient entered and dosed in extension

2) AEs occurring on or after first dose in extension and

   a) on or before last visit date, if patient discontinued the Extension phase study

   b) on or before last dose date, if patient completed the Extension phase study

Overall:

AEs occurring on or after first dose date and

a) on or before last visit date if patient discontinued the Core or Extension phase study

b) on or before last dose date if patient completed the study

Note: In addition to that, if last visit date is missing and last dose is after the non-missing last visit date, then treatment emergent flag will be considered till the last dose date.

The absolute and relative frequency of patients with study drug related AEs, SAEs, AEs with an outcome of death (if data is sufficient), AEs leading to discontinuation of treatment will be also reported by cohort and overall. Proportion and 95% CI will be calculated using exact binomial method. Differences between cohorts will be assessed by means of a logistic model

with factors (time of exposure, age at baseline (tertiles), sex, number of comorbidities (General and PsA), BMI class). Tertiles will be calculated from SAS using PROC Univariate of age at baseline.

AEs will be tabulated also by System Organ Class, Preferred Term. SAEs will be summarized as well. All study drug related AEs, AEs with an outcome of death, AEs leading to discontinuation of treatment will be listed.The above reported analysis will focus on treatment emergent adverse events.

A treatment-emergent adverse event is defined as any adverse event that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment.

Non-treatment emergent adverse events will be listed separately.

Additionally, differences between cohorts in total number of AEs / SAEs/ AEs of special interest, by study period and overall, will be done with a poisson regression model adjusting over time of exposure, age at baseline (tertile), sex, number of comorbidities and BMI class.

2.8.1.1 Adverse events of special interest / grouping of AEs

Neutropenia and candida infection will be considered as adverse events of special interest.

Adverse events of special interest will be summarized by cohort and overall divided by study phase on safety set and also will be listed separately. The below events from RMP will also be summarized, if possible. Differences between cohort will be assessed by means of a logistic model with factors (time of exposure, age at baseline (tertiles), gender, total number of comorbidities, BMI class). Tertiles will be calculated from SAS using PROC Univariate of age at baseline. If identifying the below SI is difficult, all RMP related events will be summarized.

Differences between cohorts on total number of events for each group of events (if possible) reported in the RMP will be analyzed by means of a Poisson regression model adjusting per time of exposure, age at baseline (tertile), gender, BMI class and total number of comorbidities according to the table below.

The total number of comorbidities for RMP related table will be defined by presence of at least one of the comorbidities mentioned below.

Event of special interest (from RMP)		**Comorbidities to take into account in the model**
Potential Risk	**SMQ or SOC or HLT or PT (MedDRA Version 20.0)**	
Infections and infestations	SOC: Infections and infestations	Diabetes (every form) (Y/N) Previous biologic and systemic therapy (yes vs no)
Neutropenia	PT: Agranulocytosis	

	Autoimmune neutropenia Band neutrophil count decreased Band neutrophil percentage decreased Febrile neutropenia Granulocyte count decreased Granulocytes maturation arrest Granulocytopenia Granulocytopenia neonatal Idiopathic neutropenia Leukopenia Metamyelocyte count decreased Myeloblast count decreased Myelocyte count decreased Neutropenia Neutropenia neonatal Neutropenic colitis Neutropenic infection Neutropenic sepsis Neutrophil count decreased Neutrophil percentage decreased Pure white cell aplasia White blood cell count decreased	previous biologic therapy (yes vs no)
Malignant or unspecified tumours	SMQ: Malignant or unspecified tumours	SOC: "Neoplasms benign, malignant and unspecified"
Major Adverse Cardiovascular Events (MACE)	Cardiac disorders (fatal outcomes only) SOC Vascular disorders (fatal outcomes only) SOC Brain injury (fatal outcomes only) PT Lateral medullary syndrome (fatal outcomes only) PT Post procedural stroke (fatal outcomes only) PT MACE (Myocardial infarction) [AIN457] Customized, company-specific search strategy Acute myocardial infarction PT Coronary artery embolism PT Coronary artery thrombosis PT Myocardial infarction PT Papillary muscle infarction PT Post procedural myocardial infarction PT Silent myocardial infarction PT MACE (Stroke) [AIN457] Customized, company-specific search strategy Basal ganglia haemorrhage PT Basal ganglia infarction PT Basal ganglia stroke PT Basilar artery thrombosis PT Brain injury PT	Diabetes (every form) (Yes/ No) Metabolic Syndrome (Y/N) Hypertension (Y/N) Elevated glucose (>=100mg/dL) (Y/ N) Waist circumference (>=120 man; >=88 woman) SOC: "Cardiac disorders"

	Brain stem haematoma PT Brain stem haemorrhage PT Brain stem infarction PT Brain stem stroke PT Brain stem thrombosis PT Carotid arterial embolus PT Carotid artery thrombosis PT Central nervous system haemorrhage PT Cerebellar artery thrombosis PT Cerebellar embolism PT Cerebellar haematoma PT Cerebellar haemorrhage PT Cerebellar infarction PT Cerebral artery embolism PT Cerebral artery thrombosis PT Cerebral haematoma PT Cerebral haemorrhage PT Cerebral infarction PT Cerebral thrombosis PT Cerebral venous thrombosis PT Cerebrovascular accident PT Embolic cerebral infarction PT Embolic stroke PT Haemorrhage intracranial PT Haemorrhagic cerebral infarction PT Haemorrhagic stroke PT Haemorrhagic transformation stroke PT Intracranial haematoma PT Intraventricular haemorrhage PT Ischaemic cerebral infarction PT Ischaemic stroke PT Lacunar infarction PT Lateral medullary syndrome PT Moyamoya disease PT Post procedural stroke PT Putamen haemorrhage PT Stroke in evolution PT Thalamic infarction PT Thalamus haemorrhage PT Thrombotic cerebral infarction PT Thrombotic stroke PT Wallenberg syndrome PT	“Endocrine disorders” “Gastrointestinal disorders” “Hepatobiliary disorders” PT: Transient ischaemic attack Carotid arteriosclerosis Cerebrovascular accident
Immunogenicity	SOC “Immune system disorders”	
Crohn’s disease	PT “Crohn’s disease”	“Gastrointestinal disorders”
Hepatitis B reactivation	HLT “Hepatitis viral infections”	

SMQ= Standardized MedDRA Query

2.8.2 Deaths

Deaths will be separately summarized (if there are sufficient number of deaths) by cohorts and overall on the safety set. Also, listing of deaths will be provided on safety set and with relative days from first secukinumab dose.

2.8.3 Laboratory data

Summary statistics of laboratory data and absolute and changes from baseline will be provided by visit and cohort. Summaries will be provided on the following laboratory test and their parameters;

Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count.

Chemistry: Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, GGT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

Urinalysis: Specific gravity, pH. Summary table of change from baseline will not be perfomed for specific gravity, since the data captured by sites are in different ranges, which cannot be converted.

hsCRP

Patients with values above (H) or below (L) notable criteria (Table 2.8.3) will be listed and absolute and relative frequencies will be presented by visit and cohort. Laboratory values will be presented for each patient in a data listing with an indication of whether the value is above (H) or below (L) the normal reference range.

Laboratory data will also be summarized by presenting shift tables for each laboratory parameter showing the number and percentage of patients in each cohort with the most extreme post-baseline value that falls outside normal ranges by the classification of value at baseline (H/N/L).

For urinalysis of categorical variables (Glucose, Protein, Blood, WBC, RBC), summary table of number and percentage of patients by cohort and visit will be presented.

Table 2.8.3 Clinically notable laboratory abnormalities

Laboratory parameter	Criterion for notable abnormalities
Liver Function and Related Variables	
ALT (SGPT)	> 3 x Upper Limit of Normal (ULN)
AST (SGOT)	> 3 x ULN
Total bilirubin	> 2 x ULN

Alkaline phosphatase (ALP)	> 2.5 x ULN
Renal Function and Electrolyte Variables	
Serum Creatinine	> 1.5 x ULN
Potassium	> 6 mmol/L or < 3 mmol/L
Sodium	> 160 mmol/L or < 115 mmol/L
Hematology Variables	
Hemoglobin	≥ 20 g/dL decrease from baseline
Platelet count	< Lower Limit of Normal (LLN)
White blood cell count	< 0.8 x LLN
Neutrophils	< 0.9 x LLN
Eosinophils	> 1.1 x ULN
Lymphocytes	> 1.1 x ULN
Urinalysis Variable	
Protein urine dipstick	++* (* ++ is ≥ 100 mg/dL)

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Summary of normal and abnormal ECG findings at screening will be presented by cohort on Safety set.

Listing will be provided for the normal and abnormal ECG findings at screening on Safety set.

2.8.4.2 Chest X-ray

Summary of normal and abnormal Chest X-ray findings at screening will be presented by cohort on Safety set.

Listing will be provided for the normal and abnormal Chest X-ray findings at screening on Safety set.

2.8.4.3 Vital signs

Vital signs data (sitting pulse rate, sitting systolic and diastolic blood pressure) will be summarized on Safety set.

Summary statistics of vital signs and changes from baseline will be provided by visit and cohort. Clinically notable vital signs (Table 2.8.4.3) will be listed and absolute and relative frequencies will be presented by visit and cohort.

Table 2.8.4.3 Criteria for notable vital sign abnormalities

Vital sign (unit) parameter	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

2.8.4.4 Height, weight and waist

Summary statistics n, mean, median, standard deviation, first and third quartiles, minimum and maximum will be provided for weight, waist circumference and derived BMI (calculated from body weight and height) by visit and cohort including changes from baseline.

An ANCOVA model will be fitted, adjusting by sex and age, in order to evaluate differences between cohorts in weight, waist and BMI changes vs baseline at each time point.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Variables related to health-related quality of life (HR-QoL) are described below. All HR-QoL variables will be evaluated based on Safety set. Both prevalence and LOCF approach will be adopted.

Dermatology Life Quality Index

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. The higher the score, the more quality of life is impaired.

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

Changes from baseline in DLQI at each time point will be analyzed by means of a paired t-test or Wilcoxon signed-rank test, based on data distribution.

In addition, summary statistics will be provided for the number of patients achieving DLQI 0 or 1 at each time point specifying absolute and relative frequency of patients with DLQI 0/1 response. Further, comparision between baseline and each time point for proportion of patients achieving DLQI 0 or 1 will be performed using McNemar's test.

Following details to the DLQI scoring: The scoring of each question is as follows

- Very much: scored 3
- A lot: scored 2
- A little: scored 1

- Not at all: scored 0
- Not relevant: scored 0
- Question unanswered: scored 0
- Question 7: “prevented work or studying”: scored 3

The DLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The highger the score, the more quality of life is impaired.

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

The DLQI will be analyzed under six headings as follows:

- Symptoms and feelings: questions 1 and 2, score maximum 6
- Daily activities: questions 3 and 4, score maximum 6
- Leisure: questions 5 and 6, score maximum 6
- Work and school: question 7, score maximum 3
- Personal relationships: question 8 and 9, score maximum 6
- Treatment: question 10, score maximum 3

Interpretation of incorrectly completed questinnaires:

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

1. If one question is left unanswered this is scored as 0.
2. If two or more questions are left unanswered the questionnaire will not be scored.
3. If question 7 is answered ‘yes’ this will be scored 3. If question 7 will be answered ‘no’ or ‘not relevant’ but then either ‘a lot’ or ‘a little’ is ticked this will then be scored 2 or 1.
4. If two or more response options are ticked, the response option with the highest score will be recorded.
5. If there is a response between two tick boxes, the lower of the two csore options will be recored.
6. If one item is missing from a two-item subscale that subscale will note be scored.

Hospital Anxiety and Depression Scale

Descriptive statistics of HAD-A and HAD-D score at each time point with change from baseline will be provided. Changes from baseline to each time point will be analyzed by means of a paired t-test or Wilcoxon signed-rank test, based on data distribution.

The sub-scores HAD-A and HAD-D, will be displayed per class (i.e. scores ≥11 indicate the presence of anxious or depressive disorders; scores between 8-10 points are borderline abnormal, and scores of ≤7 indicate that the disorder is not present) at each time point by means of a shift table.

In addition, the prevalence of anxiety and depression will be presented on the basis of the following three criteria:

- As per the score on the corresponding sub-scores of the HAD Questionnaire
- In terms of the treatment they are receiving for anxiety/depression.
- According to both criteria.

Following details to the HADS scoring: The scoring of each question is as follows:

I feel tense or 'wound up':	**A**		**I feel as if I am slowed down:**	**D**
Most of the time	3		Nearly all of the time	3
A lot of the time	2		Very often	2
Time to time, occasionally	1		Sometimes	1
Not at all	0		Not at all	0
I still enjoy the things I used to enjoy:	**D**		**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0		Not at all	0
Not quite so much	1		Occasionally	1
Only a little	2		Quite often	2
Not at all	3		Very often	3
I get a sort of frightened feeling like something awful is about to happen:	**A**		**I have lost interest in my appearance:**	**D**
Very definitely and quite badly	3		Definitely	3
Yes, but not too badly	2		I don't take as much care as I should	2
A little, but it doesn't worry me	1		I may not take quite as much care	1
Not at all	0		I take just as much care as ever	0
I can laugh and see the funny side of things:	**D**		**I feel restless as if I have to be on the move:**	**A**
As much as I always could	0		Very much indeed	3

Not quite so much now	1		Quite a lot	2
Definitely not so much now	2		Not very much	1
Not at all	3		Not at all	0
Worrying thoughts go through my mind:	**A**		**I look forward with enjoyment to things:**	**D**
A great deal of the time	3		A much as I ever did	0
A lot of the time	2		Rather less than I used to	1
From time to time but not too often	1		Definitely less than I used to	3
Only occasionally	0		Hardly at all	2
I feel cheerful:	**D**		**I get sudden feelings of panic:**	**A**
Not at all	3		Very often indeed	3
Not often	2		Quite often	2
Sometimes	1		Not very often	1
Most of the time	0		Not at all	0
I can sit at ease and feel relaxed:	**A**		**I can enjoy a good book or radio or TV programme:**	**D**
Definitely	0		Often	0
Usually	1		Sometimes	1
Not often	2		Not often	2
Not at all	3		Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'.

The Hospital Anxiety and Depression Scale (HADS) is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression.Calculations of scores: each of the 14 items is rated on a 4-point scale:

- Yes, definitely=3
- Yes, sometimes=2
- No, not much=1
- No, not at all=0

All items except 7 and 10 are scored as Yes, definitely=3 to No, not at all=0. Items 7 and 10 are scored as ‘Yes, definitely”=0 to “No, not at all”=3.

The HADS consists of two sub-scores: the HAD-A for anxiety and HAD-D for depression; each sub-score ranges from 0 to 21 points;

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

- 0-7 =Normal
- 8-10 =Borderline abnormal
- 11-21 = Abnormal.

Correlation between HADS and PASI

A correlation between HADS subscores and PASI will be explored by means of a Spearman coefficient (or Pearson, according to the data distribution). A cross-table for PASI 90 and PASI 75 and HAD subscores ≥11 at each time point will also be provided.

Resource utilization

Data relating to health resources use will be used for the purpose of economic evaluation. Health resources use will refer to all items of assistance provided to the patients during the study.
Health care resource utilization will be assessed by combining individual patient data on number of specialist services (eg. lab tests, phototherapy), and pharmacological treatment Direct health care resource utilization will be assessed analyzing number of specialist services and pharmacological prescriptions.

The cost for all items of assistance provided to the patient and included into the economic evaluation will be calculated according to price (such as for drugs) or tariffs (such as for tests).

For the costs attribution, since costs will not be collected in the CRF, an estimate for the following health services will be reported:
– drug treatment (ie. rescue medication)
– diagnostic services

In particular, for rescue medications (methotrexate, corticosteroids), cost will be assessed according to the dosage reported in the Patient Information Leaflets (PILs), considering an average price at the time of purchase.
Specialist services (Chest X-Ray, ECG, clinical chemistry tests, hematology tests, urinalysis) costs will be derived from regional tariffs and provided in a separate excel file (modified from http://salute.regione.emilia-romagna.it/documentazione/nomenclatore-tariffario-rer/nomenclatore_tariffario.xls/view); estimate costs for one month of rescue treatment will be reported in the same excel file.

Even though cost data are typically non-normally distributed (truncated at zero and positively skewed, reflecting the fact that some patients incur high costs), the arithmetic mean and standard deviation are the most informative measures in cost analysis.

These parametric methods are known to be fairly robust to non-normality, especially if the sample size is large, however robustness for a particular data set is difficult to judge.

All analyses will be performed considered the whole sample as denominator (ie. including those patients with a value equal to zero in a specific resource or in a specific cost item); for

example, for the number (and cost) of dermatological visits, the mean will be calculated as the sum of the dermatological visits in the whole sample divided by the number of subjects of the whole sample.

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

The primary objective of this study is to evaluate the clinical response in PASI 90 at week 16 of Cw6-negative and Cw6-positive psoriatic patients. According to literature data, Cw6-positive patients will be about 60% of the entire psoriatic patient population.

From a previous study with ustekinumab (Talamonti et al. 2013) we can observe a difference in response to PASI 90 between Cw6-positive vs Cw6-negative patients of around 30%, in favor of Cw6-POS. Therefore, it is sensible to expect a response in the Cw6-negative cohort not less than 12 % respect to the Cw6-positive group. Further considerations are stated in the paragraph below.

Phase III data on secukinumab show a PASI 90 response at 16 weeks of 71%. Under the assumption that 60% of all the enrolled patient population is represented by Cw6-POS patients, we can reasonably assume to observe a proportion of patients with PASI 90 of 80% in the Cw6-POS cohort.

Under these assumptions, considering a one-side alpha level of 0.025 and a power of 80%, 365 patients (219 Cw6-POS and 146 Cw6-NEG) are sufficient to evaluate if the response in terms of PASI 90 in the Cw6-negative cohort is not less than 12% respect to the Cw6-positive cohort.

Considering a dropout rate at 16 weeks of 10% equally divided in the two studied cohorts, a total of 406 patients should be enrolled.

All calculations were done with NQuery 7.0.

A power analysis based on a different Cw6 patient distribution was made in order to facilitate patient enrollment without power-loss in the primary endpoint evaluation. Table 3-1 shows how the enrollment rate should be set free until the ratio between Cw6-POS and Cw6-NEG reaches the 1:1 rate-distribution, with a power of at least 80%.

In particular, the number of Cw6-POS evaluable patients will range from 219 to 182, whereas those in the Cw6-NEG cohort will range from 146 to 182.

Based on the table below, the enrollment in one of the two cohorts will be stopped when the target number is achieved (a maximum of 244 Cw6-POS patients will be allowed).

Table 3-1:Power analysis

Power	Ratio	Cw6	Cw6	Cw6	Cw6	Overall	Cw6	Cw6

		POS %	POS %	POS N	POS N	N	POS %	POS %
80%	0.66	60%	40%	219	146	365	244	163
80%	0.70	59%	41%	215	150	365	239	167
80%	0.72	58%	42%	212	153	365	236	170
80%	0.75	57%	43%	209	156	365	233	174
81%	0.79	56%	44%	204	161	365	227	179
81%	0.82	55%	45%	200	165	365	223	184
81%	0.85	54%	46%	197	168	365	219	187
81%	0.89	53%	47%	193	172	365	215	192
81%	0.92	52%	48%	190	175	365	212	195
81%	0.96	51%	49%	186	179	365	207	199
81%	1.00	50%	50%	182	182	364	203	203

The choice of clinically relevant differences is based on the following considerations:

As the efficacy of secukinumab has already been clinically substantiated through extensive Phase II and III programs, all patients will be treated with active drug using the same therapeutic regimen (no placebo comparison will be done).

The primary variable is the proportion of patients who reach PASI 90 after 16 weeks. This endpoint is quite challenging and much more restrictive compared to PASI 75. Only the investigator is responsible for collecting the components or scoring signs and total regional areas in the PASI assessment. Therefore, it has great internal variability, which should be taken into account.

The paper on HLA-Cw6 ustekinumab data (Talamonti M et al. 2013) revealed a striking difference between Cw6-positive and Cw6-negative patients in the proportion of PASI 90 achievements, 85.7% vs 56.5%. This difference in PASI 90 is very relevant in the daily clinical management of patients.

Considering the above statements, it seems reasonable to claim that more than halving the difference observed with ustekinumab between Cw6-positive and Cw6-negative patients, secukinumab would be an advantage in terms of efficacy for Cw6-negative patients who do not respond properly to ustekinumab and other approved biologic drugs.

Although the sample size was calculated considering only Cw6 haplotype, it is also adequate for regression models assessing differences from baseline for clinically relevant variables. In fact, the expected number of patients who reach PASI 90 at week sixteen is at least 250 (roughly 71% of 365). Therefore, using a conservative criterion of a minimum of 10 “events” for each predictor in the model, we can add up to 25 variables in the model without loss of power (Vittinghoff E et al. 2007). This model will take into account variables such as BMI, smoking, metabolic syndrome and TNF α -308 polymorphism, which, among the six existing polymorphisms, is the one most greatly affecting response to treatment with anti-TNF α drugs.

4 Change to protocol specified analyses

The following changes and additions were done in different sections of the SAP.

General:

Summaries and analyses are extended based on 72 weeks duration.

Section 2.2 Analysis sets

Analysis Sets added for clarity or additional analyses:

- All patients: all patients who signed informed consent and entered in the study, including screen failure.
- Core phase completers set: All patients who completed the Core phase visits (Week 24) are called core phase completer set.

Analysis Sets updated/ clarified (in bold):

- Safety: all enrolled patients **included in the FAS population** who were given at least one dose of study drug.
- Intent-to-treat (ITT): all patients included in the safety population with at least one post-baseline efficacy assessment and **with the Cw6 assessement**.

Section 2.3.1:

By visit disposition summary table is added.

Section 2.3.2:

P-values of comparison of cohorts will be analysed based on stratified CMH, and logistic model with covariates (for categorical variables) and ANCOVA (for continuous variables).

Total number of comorbidities (all medical histories) between cohorts will be analyzed by Poisson model adjusted by covariates.

Section 2.4.2:

Previous psoriasis therapies will be analysed by logistic model and total number of such therapies will be analysed by Poisson model after adjusting for covariates.

Section 2.5:

The model factors are clarified in the SAP.

Non-responder imputation is added. Analsyses based on NRI for primary and secondary efficacy endpoints are added.

Modelling approaches of PASI scores and IGA scores have been included based on MMRM. Modelling of IGA0/1 responder is also added.

Section 2.8.1

The AEs comparison of cohorts will be done based on CI and pvalues generated from logistic model or poisson model (for total number of events overall).

The AESI of RMP related events will be summarized and compared based on logistic model approach.

Section 2.8.4

ANCOVA model for vital signs are added.

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 **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	

Relationship		Time imputation
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 cuptured 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

Not applicable.

5.1.2.2 Post therapies date imputation

Not applicable.

5.1.2.3 Other imputations

Not applicable.

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

The SAS procedure PROC LOGISTIC, will be used to perform Logistic regression with the following sample SAS code:

```
PROC LOGISTIC DATA = .... ;
CLASS usubjid acenter trtpn region smkst bmi .. / param=glm;
MODEL aval = trtpn region smkst bmi bl..;
LSMEANS trtpn / diff cl exp;
Ods output diffs=lsm_diff;
RUN;
```

In cases where separation is a concern, e.g. 0% response in one cohort, an exact logistic regression model will be applied. To ensure convergence, this model will not include any continuous covariates.

PROC LOGISTIC DATA = ... exactonly;

CLASS usubjid acenter trtpn region smkst bmi .. / param=glm;

MODEL aval = trtpn region smkst bmi bl..;

EXACT trtpn / estimate=both;

Ods output exactoddsratio=exactoddsratio;

RUN;

The SAS procedure PROC FREQ using Z-test with riskdiff option, will be used to derive Confidence intervals for response rates with the following sample SAS code:

PROC FREQ DATA = ...;

BY visit;

TABLES trtan*resp / riskdiff;

RUN;

From above code, we can get confidence interval for difference of proportion in PASI90 response between cohorts and also Confidence interval for proportion of PASI90 for individual cohort.

5.4.2 Key secondary analysis

Not applicable.

5.4.3 Secondary analysis

The SAS procedure PROC FREQ with Method= NEWCOMBE option, will be used to derive Confidence intervals for response rates with the following sample SAS code:

PROC FREQ DATA = ...;

BY visit;

TABLES trtan*resp / riskdiff (column=2 cl=(NEWCOMBE));

RUN;

The SAS procedure PROC MIXED will be used for linear mixed model for repeated measurements (MMRM) analysis with the following sample SAS code:

PROC MIXED DATA=dataset noclprint;

CLASS cohort vis1n usubjid MissingPattern;

MODEL Changes= cohort week0 dropout visit prop_score

cohort*visit cohort*MissingPattern;

REPEATED visit/subject=usubjid TYPE=cs;

LSMEANS cohort*visit/pdiff cl;

RUN;

The SAS procedure PROC PHREG, will be used to perform computed using a stratified Cox proportional hazards regression model with Cw6 group and baseline PASI as explanatory variable with the following sample SAS code:

PROC PHREG DATA=....;

CLASS trtpn baseline ..;

MODEL var*censor(0)= trtpn base.../rl ties=efron ;

RUN;

The SAS procedure PROC LIFETEST, will be used to perform log-rank test and to plot Kaplan-Meier estimates of the cumulative rate for each cohort with the following sample SAS code:

PROC LIFETEST DATA=... PLOT;

TIME timevar*censor(0);

STRATA...;

RUN;

The SAS procedure PROC CORR, will be used to perform Spearman's (or Pearson's product moment correlation depending on data distribution) correlation with the following sample SAS code:

PROC CORR DATA = ... pearson/spearman OUTP=CORR;

VAR VAR1 VAR2;

RUN;

The SAS procedure PROC UNIVARIATE with NORMAL option, will be used to check the normality with the following sample SAS code:

PROC UNIVARIATE DATA = ... normal;

VAR var.../options...;

CLASS var;

RUN;

The SAS procedure PROC UNIVARIATE, will be used to perform Wilcoxon signed rank test with the following sample SAS code:

PROC UNIVARIATE DATA = ...;

VAR var...;

RUN;

The SAS procedure PROC TTEST, will be used to perform paired t-test with the following sample SAS code:

PROC TTEST;

PAIRED VARbefore*VARafter;

RUN;

The SAS procedure PROC FREQ with EXACT statement equal to MCNEM or AGREE will be used to perform Mc Nemar's test with the following sample SAS code:

PROC FREQ DATA = ...;

TABLES trtan*resp ;

EXACT MCNEM or AGREE;

RUN;

SAS code for poisson regression model

proc genmod data=demo_ae ;

class cw6 sex age_group/ param = glm;

model numev = cw6 age_group sex / type3 dist=poisson;

lsmeans cw6 /ilink cl diff;

lsmeans age_group /ilink cl diff;

lsmeans sex /ilink cl diff;

run;

proc genmod data=demo_ae ;

class cw6 (param = ref ref = "NEGATIVE") sex (param = ref ref = "M") age_group (param = ref ref = "<=40 years");

model numev = cw6 age_group sex / type3 dist=poisson ;

estimate "IRR Cw6 (POS vs NEG) " cw6 1 -1;

estimate "IRR Age (>40 vs <=40)" age_group 1 -1;

estimate "IRR Sex (Female vs Male)" sex 1 -1;

run;

PASI Changes vs baseline: Linear Mixed Model for Repeated Mesurements (MMRM):

The SAS procedure PROC MIXED will be used in the analysis, in particular:

```
proc mixed data=dataset noclprint;
 class cohort vis1n usubjid MissingPattern;
 model Changes= cohort week0 dropout visit prop_score
            cohort*visit cohort*MissingPattern;
 repeated visit/subject=usubjid type=un;
 lsmeans cohort*visit/pdiff cl;
run;
```

where changes includes all changes vs week 0 of PASI; the dropout variable is the missing pattern (i.e. a categorical variable with values of 1, 2, 3 etc.. representing completers, 1 assessment missing, 2 assessments missing, 3 assessement missing etc. in considered dependent variable –e.g. PASI); the prop_score variable is the propensity score. In order to take all the confounding factors into account, the propensity score methodology will be applied and will be included in the final model, as described above. Propensity score will be derived using logistic regression model considering cohort as the dependent variable and baseline covariates as the factors in the model. The derived propensity score will be used as the covariate in the MMRM model.

MMRM with MI approach

Multiple imputation will be performed in SAS using the following three-stage approach:

PROC MI will be applied for each PASI change (or each post baseline PASI score) containing some missing values, which results in creation of multiple copies of this dataset. All copies contain identical values of the non-missing data items, but different values imputed for missing items. The following SAS statement will be used:

```
proc mi data=PASI_in out=PASI_out seed=1425;
var cohort Baseline PASI score PASI score at week 1 PASI score at week 2 PASI score at week 3 PASI score at week 4 PASI score at week 8 PASI score at week 12 PASI score at week 16 PASI score at week 20 PASI score at week 24;
class cohort;
monotone regression;
run;
```

where variables PASI score at week 1 PASI score at week 2 PASI score at week 3... PASI score at week 24 contain missing values for some patients at each PASI time point, which PROC MI will impute using linear regression models.

Then we can calculate changes vs. baseline at each time point

```
data PASI_in_out1;
set PASI_out;
visit=”Week 1”; change= PASI score at week 1 – Baseline PASI score; output;
visit=”Week 2”; change= PASI score at week 2 - Baseline PASI score; output;...
visit=”Week 24”; change= PASI score at week 24 - Baseline PASI score; output;
run;
```

and then we will perform the ANCOVA model using the following statement:

```
proc mixed data= PASI_in_out1;
by visit;
class <As required factors >;
model change =<As per reqired covarites> /;
lsmeans treatment /diff pdiff cl;
ods output diffs=diff_MI lsmeans=LSM_MI;
run;
```

where prop_score is the same continuous variable used for the primary model.

Results of the ANCOVA analysis on 500 imputed dataset will be combined to derive an overall results using the following code:

```
proc mianalyze parms(classvar=full)=diff_mi;
class cohort;
modeleffects cohort:
 ods output parameterestimates=DIFF_MIAN;
by visit;
run;
```

```
proc mianalyze data=lsm_mi;
class cohort;
modeleffects cohort:
 ods output parameterestimates=LSM_MIAN;
by visit;
run;
```

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause patients to be excluded

Deviation ID	Description of Deviation (DVTERM)	Exclusion in Analyses	Severity code
INCL01	Informed consent missing or not signed prior to initiating study procedures.	EXCLUDE FROM FAS ITT SAF PP	6
INCL02	"Calculated Age" is expected to be equal or greater than 18 years or age is missing.	EXCLUDE FROM PP	4
INCL03A	Date of diagonosis of plaque type psoriasis is missing or difference between date of plaque type psoriasis and date of Visit date at Week 0 is less than 6 months	EXCLUDE FROM PP	4
INCL3B	Subject has psoriatic arthritis however does not satisfy classification criteria as per CASPAR.	EXCLUDE FROM PP	4
INCL04	Patient is a violator if: - PASI less than 10 - PASI greater than 5 but less than 10 and DLQI less than 10	EXCLUDE FROM PP	4
INCL05	Patients candidate for systemic therapy, treatment naive or failed response to at least one systemic therapies	EXCLUDE FROM PP	4
EXCL02	Cyclosporine or methotrexate administration within 4 weeks prior to Day 1.	EXCLUDE FROM PP	4
EXCL03	Anti-TNF alpha therapy within timelines depending on drug half-life.	EXCLUDE FROM PP	4
EXCL04	Previous exposure to secukinumab or any other biologic drug targeting IL-17 or the IL-17 receptor	EXCLUDE FROM PP	4
EXCL05	Previous exposure to ustekinumab or any other biologic drug for the treatment of psoriasis that is not anti-TNF alpha therapy.	EXCLUDE FROM PP	4
EXCL06	Intravenous or intramuscular steroids within 2 weeks prior to screening and during screening.	EXCLUDE FROM PP	4
EXCL07	Ongoing use of corticosteroid topical treatments or UV therapy.	EXCLUDE FROM PP	4
EXCL15	Underlying condition that, in the opinion of Investigator, would pose a risk to subject safety or interfere with study evaluation, procedures and completion.	EXCLUDE FROM PP	4
EXCL16	Abnormal laboratory results at screening:	EXCLUDE FROM PP	4

Deviation ID	Description of Deviation (DVTERM)	Exclusion in Analyses	Severity code
	Liver tests: AST, ALT or ALP greater than 2.0 × ULN or total bilirubin greater than 1.5 × ULN (except for subjects with Gilbert Syndrome).		
EXCL19	Subject is currently enrolled in another investigational study.	EXCLUDE FROM PP	4
OTH08	PASI 50 not achieved at Week 16 however patient continued in the study.	EXCLUDE FROM PP	4
COMD01	Use of Prohibited medication (Ustekinumab as prior psoriasis therapy)	EXCLUDE FROM PP	4
COMD03	Use of Prohibited medication (Alefacept as prior psoriasis therapy)	EXCLUDE FROM PP	4
COMD05	Use of Prohibited medication (Etanercept as Prior Psoriasis Therapy)	EXCLUDE FROM PP	4
COMD07	Use of Prohibited medication (Adalimumab as Prior Psoriasis Therapy)	EXCLUDE FROM PP	4
COMD09	Use of Prohibited medication (Infliximab as Prior Psoriasis Therapy)	EXCLUDE FROM PP	4
COMD11	Use of Prohibited medication (Golimumab as Prior Psoriasis Therapy)	EXCLUDE FROM PP	4
COMD16	Use of Prohibited medication (Phototherapy as Prior Psoriasis Therapy)	EXCLUDE FROM PP	4
COMD18	Use of Prohibited medication (Other systemic psoriasis treatments)	EXCLUDE FROM PP	4
COMD19	Use of Prohibited medication (Topical treatment that is likely to impact signs and symptoms of psoriasis)	EXCLUDE FROM PP	4
COMD02	Use of Prohibited medication (Ustekinumab taken concomitantly)	EXCLUDE FROM PP	4
COMD04	Use of Prohibited medication (Alefacept taken concomitantly)	EXCLUDE FROM PP	4
COMD06	Use of Prohibited medication (Etanercept taken Concomitantly)	EXCLUDE FROM PP	4
COMD08	Use of Prohibited medication (Adalimumab taken concomitantly)	EXCLUDE FROM PP	4
COMD14	Use of Prohibited medication (Phototherapy taken concomitantly)	EXCLUDE FROM PP	4
COMD17	Use of Prohibited medication (Other systemic immunomodulating treatments)	EXCLUDE FROM PP	4
OTHER	No secukinumab administration	EXCLUDE FROM ITT SAF PP	2
OTHER	No valid PASI assessment after baseline	EXCLUDE FROM ITT PP	4

Deviation ID	Description of Deviation (DVTERM)	Exclusion in Analyses	Severity code
OTHER	Patient who didn't complete the study	EXCLUDE FROM PP	4
OTHER	Patient's without Cw6 assessment	EXCLUDE FROM ITT PP	5

Table 2 Subject Classification rules

Analysis set	PD Population Codes that cause patient to be excluded	Non-PD criteria that cause a patient to be excluded
FAS	1,3	
ITT	1,2, 4, 5	NA
Per-protocol	1,2,4, 5, 6	Not in ITT
Safety	1,2, 3, 6	No study drug taken

6 Reference

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