NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457A2318 / NCT03066609

A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab, to demonstrate efficacy after twelve weeks of treatment and to assess safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity

Statistical Analysis Plan (SAP)

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Date	Reason for update	Section and title impacted (Current)
22-Feb-2017	Final	
5-Dec-2017	Protocol amendment	Primary endpoint analysis added for authority interactions for 2.14 part
	Imputation rule updated	First diagnosis date of PSO and PsA were added in 5.14 part
7-Feb-2018	Analysis set update	Detailed information of analysis set during different treatment period were added in 2.2 part
	Baseline PsA removed from analysis model	Baseline PsA was removed from the analyses models since too few subjects with baseline PsA, part 2.5 and 2.6 were impacted.
11-Jan-2019	Amendment final	Section 4 Change to protocol specified analyses
		Added the definition of Entire study period.
		[redacted]

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BSA	Body surface area
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
[redacted]	[redacted]
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

Data will be analyzed by Novartis 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.

This document covers statistical and analytical plans for CAIN457A2318 study with reference to the study protocol (version 01 - amended protocol) and the project standard analysis plans (AIN457A MAP).

1.1 Study design

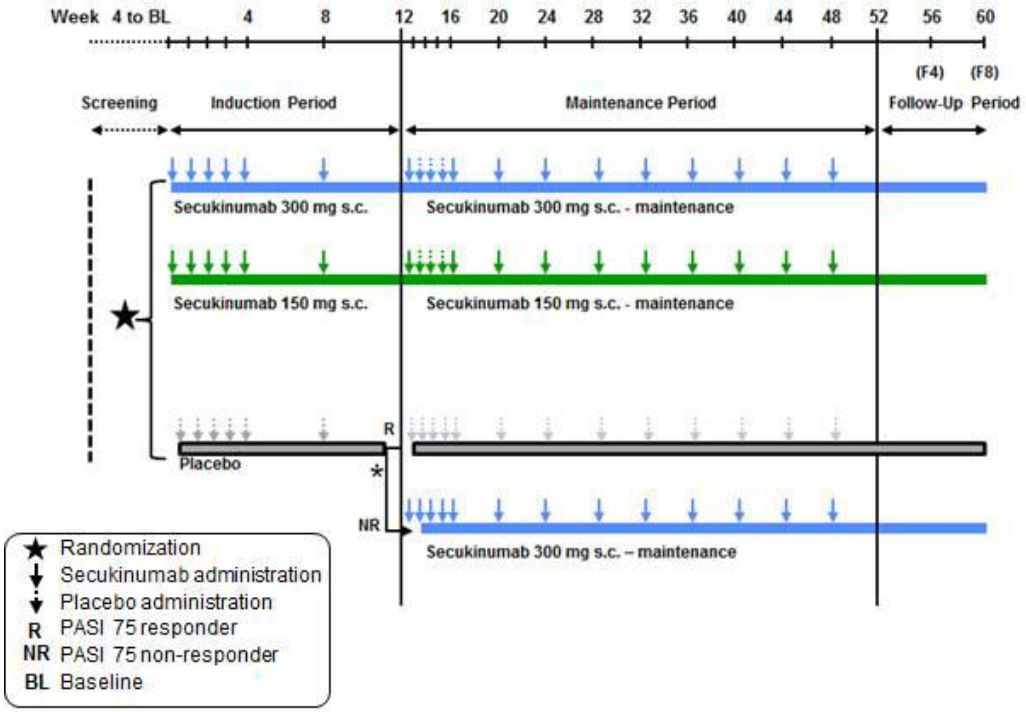
This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 536 subjects with moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis comorbidity. The efficacy and safety data from this global study will primarily be used to support the registration of secukinumab in China.

Randomization will be stratified by geographical region and presence of psoriatic arthritis at baseline. Subjects will be randomized using a 2:1:1 ratio into one of the treatment groups:

- Secukinumab 300 mg regimen group: secukinumab 300 mg s.c. (two injections of secukinmab 150 mg) once weekly for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 and until Week 48, except for weeks 13, 14, and 15 where they will receive a weekly dose of placebo to maintain the blind.
- Secukinumab 150 mg regimen group: secukinumab 150 mg s.c. (one injection of secukinumab 150 mg and one injection of placebo matching secukinumab 150 mg) once weekly for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks, starting at Week 4 and until Week 48. Similar procedure as in the 300 mg group will be performed at week 13, 14, 15 to maintain the blind.
- Placebo group: placebo secukinumab (two injections of placebo matching secukinumab 150 mg) once per week for four weeks (at Baseline, Weeks 1, 2, and 3), followed by dosing every four weeks till week 8. Prior to receiving the Week 12 dose, PASI 75 responders in the placebo group will be assigned to the placebo group and receive placebo from Week 12 till week 48; the PASI 75 non-responders will be reassigned to 300 mg secukinumab regimen group and receive their treatment from Week 12 till week 48.

The study consists of four epochs: Screening (of at least 1 week and up to 4 weeks), Induction (of 12 weeks), Maintenance (of 40 weeks), and Follow-up epoch (of 8 weeks).The study design is presented in Figure 3-1.

Figure 3-1 Study design



For ongoing review of safety information an internal Data Monitoring Committee (DMC) is established.

In addition, a primary endpoint analysis is planned after all subjects have completed their Week 16 visit. Full analysis of all data will be performed at the end of the study.

1.2 Study objectives and endpoints

The primary objective of this study is to demonstrate the superiority of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis in terms of both PASI 75 and IGA mod 2011 0 or 1 response (co -primary endpoints) at Week 12 compared to placebo.

The secondary objectives are :

- To demonstrate the superiority of secukinumab in terms of PASI 90 response at Week 12 compared to placebo.
- To assess the efficacy of secukinumab in terms of:
    - maintaining PASI 75 response at Week 52 in subjects who were PASI 75 responders at Week 12
    - maintaining IGA mod 2011 0 or 1 response at Week 52 in subjects who were IGA mod 2011 0 or 1 responders at Week 12.
    - PASI 50/75/90/100 response over time up to week 12 and week 52
    - IGA mod 2011 0 or 1 response over time up to week 12 and week 52
    - PASI score over time up to week 12 and week 52
    - IGA mod 2011 score over time up to week 12 and week 52
    - Time to PASI 75 response up to Week 12

In addition, the study will assess efficacy of secukinumab in treating subjects with psoriatic arthritis comorbidity in terms of ACR 20/50/70 response and ACR components at Week 12 compared to placebo and over time until Week 52. The study will also assess the safety and tolerability of secukinumab with prefilled syringe in the patient population over the study period.

The efficacy and safety data from this global study will primarily be used to support the registration of secukinumab in China, for the treatment of moderate to severe chronic plaque-type psoriasis and psoriatic arthritis comorbidity.

The efficacy variables are summarized as below:

Table 1-1 Primary, secondary and exploratory variables

Variable	Type
PASI 75 response @ Week 12 (compared to placebo)	primary
IGA 0/1 response @ Week 12 (compared to placebo)	primary
PASI 90 response @ Week 12	key secondary
PASI 75 response @ Week 52 for PASI 75 responders at Week 12	secondary
Loss of PASI 75 response for PASI 75 responders at Week 12	secondary
IGA 0/1 response @ Week 52 for IGA 0/1 responders at Week 12	secondary
Loss of IGA 0/1 response for IGA 0/1 responders at Week 12	secondary
PASI 50/75/90/100 response over time up to week 52	secondary
IGA 0/1 response over time up to week 52	secondary
PASI score over time up to week 52	secondary
IGA mod 2011 categories over time up to week 52	secondary
Time to PASI 75 response up to Week 12	secondary
ACR 20/50/70 response in subjects with psoriatic arthritis over time up to week 52	secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the week 16 and final analyses. Statistical software SAS verion 9.4 or later will be used. For week 16 analysis, data will be presented till week 16 visit. This analysis will include primary endpoint data analysis at Week 12 visit.

Regarding the DMC analyses, a vendor - [redacted] will help with part of the work based on the internal resource and workload.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

If not otherwise specified, p-values will be presented for two-sided hypothesis testings and two-sided confidence intervals will be displayed. Unless otherwise stated, the level of significance will be set to 5% (two-sided).

All listings will be presented by treatment sequence.

Footnotes on outputs will be kept to a minimum.

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings in Appendix 16.2 can be presented on a separate page and do not have to be repeated as footnotes on each listing
- sorting order of categories, e.g. for sorting within MedDRA (Medical Dictionary for Regulatory Activities) hierarchy levels
- MedDRA version used for reporting of MedDRA coded data

Footnotes will generally NOT be given for

- units displayed on the output
- interpretation of results (e.g. “odds ratio larger 1 favors active treatment”)
- information that can be retrieved from the statistical section of the clinical study report (CSR) unless it is not identifiable from the output, e.g.
  - explanation of analysis model used unless results of more than one model are displayed on an output
  - derivations of variables (e.g. BMI will not be explained on a footnote)
- information that will be provided in the clinical study protocol and/or methods section of the CSR (e.g. baseline definition if this is specified in the statistical section of the CSR)

2.1.1 General definitions

2.1.1.1 Study treatment

The following study drugs will be used:

- Investigational treatment
  - Secukinumab 150 mg: 1 ml liquid formulation in a pre-filled syringe
  - Secukinumab 300 mg: 2 pre-filled syringes each containing 150mg/ml liquid formulation
- Control treatment
  - Placebo, 1 ml liquid formulation in a pre-filled syringe

2.1.1.2 Study Day 1 and other study days

The first day of administration of randomized study treatment (first dose) is defined as Study Day 1 or Day 1.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose]+1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before

Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in [Programming Datasets Specifications (PDS)].

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

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

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

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the CRF. The subject's exposure will be calculated considering the end of treatment period visit (e.g., treatment completion visit). The end of treatment period will be defined as the last dose plus 84 days or last visit whichever occurs earlier. i.e., for subjects who discontinued or have their last visit earlier than last dose plus 84 days, the end of study treatment exposure will be the date of the last study visit in the corresponding treatment period.

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

2.1.1.5 Visit window

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-1. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments, and the days are counted since the date of randomization for efficacy assessments.

These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 60 instead of on Day 29, it will be re-aligned to visit window *Week 12*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

Table 2-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-88
Week 13	13	92	89-95
Week 14	14	99	96-102
Week 15	15	106	103-109
Week 16	16	113	Day 110-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183
Week 28	28	197	Day 184-211
Week 32	32	225	Day 212-239
Week 36	36	253	Day 240-267
Week 40	40	281	Day 268-295
Week 44	44	309	Day 296-323
Week 48	48	337	Day 324-351
Week 52	52	365	Day 352-379
Week 56	56	393	Day 380-407
Week 60	60	421	Day 408-435

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments.

For parameters which are not collected at every visit (e.g. [redacted] HAQ-DI), visit windows defined in Table 2-1 will be combined. For example, if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 88 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 89 to Day 183 (combining Week 13 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.1.1.6 below are applied.

For studies with re-randomization at the end of induction period or treatment epoch 1, assessments from maintenance period (or treatment epoch 2) will not be considered for induction period (or treatment epoch 1), e.g. if a Week 13 (scheduled visit) measurement would fall into the Week 12 visit window, this measurement would not be analyzed as induction period value. Of note, for subjects who discontinue in induction period, i.e. not moving into maintenance period, measurements taken in follow-up period would still be considered for induction period.

Of note: subject's height assessed during screening will not be remapped according to the analysis visit window.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window (after Day 435) it is not assigned an analysis visit and will be listed under label "After Week 60".

2.1.1.6 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 (See Table 2-2).

For baseline assessment definition see Section 2.1.1.3. 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 90 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 within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3.
Post-baseline efficacy	All data except PRO, e.g., PASI, IGA	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurement are taken on the same day then select the first one using eCRF visit number. If two measurement have been taken on the same day and same visit then select the worst.

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

2.2 Analysis sets

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

Randomized set: The randomized set will be defined as all subjects who were randomized at baseline visit. Unless otherwise specified, misrandomized subjects will be excluded from the randomized set.

Misrandomized subjects are subjects who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed, however have not been treated. If subjects were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned in the last randomization.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual randomization stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

Of note, subjects excluded from the randomized set will be excluded from the FAS.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. Subjects will be analyzed according to treatment received.

The treatment received will be set to the treatment randomized. But if a subject has received the wrong treatment during the entire study, the treatment received will be set to this wrong treatment.

For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared displaying adverse events occurred after the treatment errors.

The following study periods will be considered for analysis:

- **Screening** period (before Randomization)
- **Induction** period (Randomization to Week 12 pre-dose)
- **Maintenance** period (Week 12 -dose to Week 52)
- **Entire treatment** period = Induction period + Maintenance period (Randomization to Week 52)
- **Follow-up** period (Week 52 to Week 60)
- **Entire study period** = Induction period + Maintenance period (Randomization to Week 52) + **Follow-up** period (Week 52 to Week 60)

2.2.1 Subgroup of interest

The co-primary endpoints and important secondary endpoints will be evaluated using the subgroups defined in Table 2-3. Subgroup analyses for the study endpoints are represented in Table 2-4.

If IRT mis-classify the stratrum, such as baseline psoriatic arthritis, the correct stratum will be derived based on baseline information and protocol deviation data. The correct stratum may be used for subgroup analysis.

Table 2-3 Subgroup definitions

Subgroup variables	Categories	Description	Label for outputs	Suffix for outputs*
Randomization region stratum	China, Non-China	All outputs will be repeated for Chinese patient	Region stratum	c
Randomization stratum of psoriatic arthritis at baseline	Yes, No		Baseline PsA stratum	a
Weight category	body weight category (< 70 kg, >=70 and <90 kg, >=90 kg)		Weight category	b
Previous systemic therapy	Yes, No		Previous systemic therapy	d

Subgroup variables	Categories	Description	Label for outputs	Suffix for outputs*
* Suffixes will be used for the outputs numbering, see [TFL shell document]				

Table 2-4 Subgroup analyses

Endpoint/analysis	Randomization stratas	Weight category	Previous psoriasis therapy*
Co-primary endpoints:			
PASI 75 response @ Week 12	X	X	X
IGA 0/1 response @ Week 12	X	X	X
Secondary endpoints:			
PASI 90 response @ Week 12	X	X	X
PASI 50/75/90/100 response over time up to week 52	X	X	X
IGA 0/1 response over time up to week 52	X	X	X

Note: presented are only those endpoints that need subgroup analyses.

*: only for “Previous <biologic/systemic/non-biologic systemic> therapy” and embedded subgroup “failure” and non-biologic therapy failure “at least two failures”.

2.3 Patient disposition, demographics and other baseline characteristics

The summaries will be shown for the following treatment groups:

- AIN457 300 mg, AIN457 150 mg, Placebo, Placebo - AIN 457 300mg, Placebo - Placebo, Total

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age (which is derived from year of birth and the Informed consent date)
- Height
- Weight
- Body mass index (BMI)

Categorical variables:

- Region categories (China, non-China)
- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity
- Smoking status at baseline
- Weight categories (<70 kg, >=70 and <90 kg, >= 90 kg)

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

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

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

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

Psoriasis specific baseline characteristics and history of disease will be summarized as well:

Continuous variables:

- Baseline PASI
- Baseline total BSA
- Baseline ACR (American College of Rheumatology) components
- Baseline tender joint count
- Baseline swollen joint count
- Baseline CRP (hsCRP)
- Baseline HAQ-DI score
- Time since diagnosis of psoriasis
- Time since diagnosis of psoriatic arthritis

Categorical variables:

- Baseline PASI categories (≤20, >20)
- Baseline IGA mod 2011 score categories (at least mild, moderate, severe)
- Severity of psoriasis categories (CHMP guidelines, mild (total BSA <10% and PASI < 10) , moderate ((PASI ≥10 or total BSA≥10%) and PASI ≤20 and total BSA ≤20%), severe (total BSA >20% or PASI > 20))
- Baseline psoriatic arthritis categories (yes, no)
- Previous exposure to biologic systemic psoriasis therapy (yes, no)
- Previous exposure to systemic psoriasis therapy (yes, no)
- Previous exposure to non-biologic systemic psoriasis therapy (yes, no)
- Previous failure to biologic systemic psoriasis therapy (yes, no)
- Previous failure to systemic psoriasis therapy (yes, no)
- Previous failure to non-biologic systemic psoriasis therapy (including phototherapy and photo- chemotherapy) (yes, no)

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the randomized set.

Any condition entered on the *Relevant medical history / current medical conditions* CRF (including family history) will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

Summaries for cardiovascular medical history will be summarized by categories.

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set who completed study periods, the entire study and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

Of note, patients completed all the epochs planned in the protocol are defined as completers for the entire study.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

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

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain time thresholds will be displayed. The following categories will be presented: “any exposure”, “≥1 week” “≥4 weeks”, “≥8 weeks”, “≥12 weeks”, “≥16 weeks”, “≥20 weeks”, “≥24 weeks”, “≥28 weeks”, “≥32 weeks”, “≥36 weeks”, “≥40 weeks” “≥44 weeks”, “≥48 weeks”, and “≥52 weeks”.

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

Duration of exposure (days) = min (‘end of treatment period’ date, last dose date +84) – first dose date +1

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

Duration of exposure (100 subject years) = duration of exposure (years) / 100

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by treatment group for the safety set unless otherwise specified. Concomitant treatments will be displayed for the treatment period.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment, and last dose plus 84 days or last (including follow-up visits) whichever occurs

earlier will be a **concomitant** medication, including those which were started pre-baseline and continued into the treatment period.

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

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Further rules will be given in Section 5.

2.5 Analysis of the primary objective

2.5.1 Primary and key secondary endpoints

The co-primary efficacy variables are PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12. The key secondary endpoint is PASI 90 response at week 12. The analysis of the co-primary and key secondary variables will be based on the FAS.

2.5.1.1 Definition of PASI and related variables

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

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 2-8.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 2-6. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

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

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

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

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

The investigator is responsible for collecting the components or scoring signs and total surface area (BSA) for all visits. PASI will be done by investigator at randomization and week 12 only; The PASI scores at other visits will be calculated by Novartis and will be used in the analysis and for derivation of PASI response values (see below). In addition, the investigator will determine PASI75 responder status at Week 12.

Table 2-5 The PASI scoring system

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

* Percentage (not score) of body region (not whole body) affected will be entered in the eCRF.
† Neck is assessed as part of the Head (H) body region.
‡ Axillae and groin are assessed as part of the Trunk (T) body region.
§ Buttocks are assessed as part of the Lower limbs (L) body region.

The following definitions are possible efficacy evaluations that can be used in clinical trials in psoriasis (CHMP/EWP/2454/02, 2004):

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

[redacted]

[redacted]

2.5.1.2 Definition of IGA mod 2011 score and IGA mod 2011 0 or 1 response

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 2-6) has been developed based on a previous version of the scale used in secukinumab phase II studies, and has been updated in collaboration with health authorities (in particular the FDA). The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points. It is recommended that the same evaluator conducts the assessments throughout the study whenever possible.

The IGA mod 2011 used in this study is static, i.e., it refers exclusively to the subject's disease state at the time of the assessments, and does not attempt a comparison with any of the subject's previous disease states, whether at baseline or at a previous visit.

Table 2-6 The IGA mod 2011 rating scale

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling.
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions.

Note: Involvement of nails is not part of the assessment.

Subjects require an IGA mod 2011 score at randomization of 3 or 4 in order to participate in the study. Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA mod 2011 scale compared to baseline.

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypotheses for PASI 75 response at Week 12 and IGA mod 2011 0 or 1 response at Week 12 being tested is that any of the secukinumab groups are not superior to placebo in the proportion of subjects with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

Let pj denote the proportion of PASI 75 responders at Week 12 for treatment group *j* and rj denote the proportion of IGA mod 2011 0 or 1 responders at Week 12 for treatment group *j*, *j*=0, 1, 2, where

□□0 corresponds to placebo,
□□1 corresponds to secukinumab 150 mg,

□□2 corresponds to secukinumab 300 mg.

The following hypotheses will be tested

H1: p1 – p0 ⩽ 0 versus HA1: p1 – p0 > 0,
H2: p2 – p0 ⩽ 0 versus HA2: p2 – p0 > 0,
H3: r1 – r0 ⩽ 0 versus HA3: r1 – r0 > 0,
H4: r2 – r0 ⩽ 0 versus HA4: r2 – r0 > 0.

In other words:

H1: secukinumab 150 mg is not superior to placebo with respect to PASI 75 response at Week 12
H2: secukinumab 300 mg is not superior to placebo with respect to PASI 75 response at Week 12
H3: secukinumab 150 mg is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12
H4: secukinumab 300 mg is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

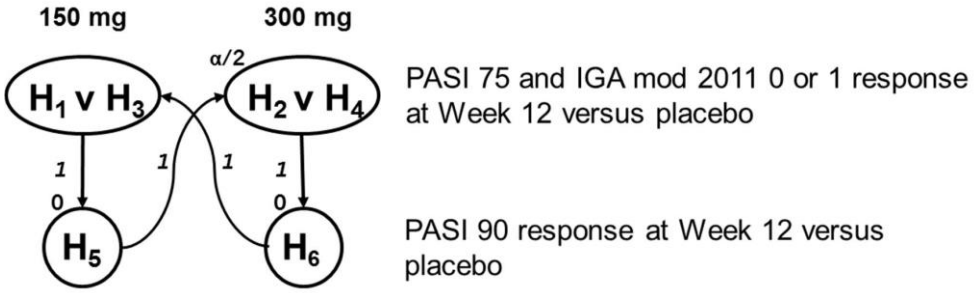
The primary endpoint (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) will be evaluated using alogistic regression model with treatment group, baseline body weight category, geographical region, and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo. In case of the logistic regression does not converge due to low reponse rates in the placebo group, an exact logistic regression with be performed and the detailed analysis is described in Section 5.4.2. In case of rates of 0% or 100% in one of the treatment groups, confidence intervals and p-values from the t-test for the risk difference comparing to 0 will be provided for the analyses using multiple imputation; for the analyses using non-responder imputation, Fisher's exact test will be performed and confidence intervals for risk difference will be provided.

PASI 90 response at Week 12 will be evaluated analogously to PASI 75 and IGA mod 2011 0 or 1 response at Week 12 (i.e., logistic regression analysis) and the following hypotheses will be tested:

H5: secukinumab 150 mg is not superior to placebo with respect PASI 90 response at Week 12
H6: secukinumab 300 mg is not superior to placebo with respect PASI 90 response at Week 12

The graphical approach of Bretz et al. 2009 for sequentially rejective testing procedures is used to illustrate the testing strategy:

Figure 2-1 Testing strategy



One-sided p-values will be derived. The family-wise error will be set to α =2.5% (one-sided). The hypotheses are mapped into two sets (H1, H3, and H5) or (H2, H4, and H6) such that hypotheses within a set correspond to the same secukinumab dose regimen (150 mg or 300 mg). In essence, the type-I-error probability will be equally split for both sets of hypotheses and within each set the hypotheses are tested sequentially as follows:

Within each pair of hypotheses (H1 or H3) and (H2 or H4) each hypothesis is tested at α /2. Only if both hypotheses of a pair are rejected, the testing sequence will continue and the PASI 90 comparisons of secukinumab versus placebo are tested, H5 or H6 will be tested at α /2 (one-sided).

If all hypotheses within a set referring to a secukinumab dose regimen have been rejected, i.e., (H1, H3, and H5) or (H2, H4, and H6), the corresponding type-I-error probability can be passed on to the other group of hypotheses, and if needed, hypotheses can be retested at a new significance level.

2.5.3 Handling of missing values/censoring/discontinuations

Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputation (MI) as primary imputation method for the missing values.

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

Non-responder imputation will be used as a sensitivity method: Missing values with respect to response variables based on PASI score and IGA 2011 categories 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 of the study prior to last scheduled visit and being responder 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 as responder for visit x, except for the missing data at last visit in the treatment period.

2.5.4 Supportive analyses

Sensitivity analyses will be performed as follows:

Co-primary endpoints (PASI 90 and IGA 0 or 1 response at Week 12) and key secondary endpoints will be evaluated using the logistic regression as described in primary analysis method with non-responder imputations instead of multiple imputation for missing values.

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Secondary endpoints

2.6.1.1 Maintenance of PASI 75 response after 52 weeks of treatment

Summary statistics as well as 95% confidence intervals will be presented for maintenance of PASI 75 response at Week 52 for the subset of subjects with PASI 75 response at Week 12 in the secukinumab treatment groups.

In addition, Kaplan-Meier estimates including 95% confidence intervals for cumulative rate of subjects losing PASI 75 response up to Week 52 will be calculated for the subset of subjects with PASI 75 response at Week 12 in the secukinumab treatment groups.

2.6.1.2 Maintenance of IGA 0 or 1 response after 52 weeks of treatment

The same analyses as planned for maintenance of PASI 75 response will be performed for IGA 0 or 1 response after 52 weeks of treatment, but analyses will be based on the subset of subjects with IGA 0 or 1 response at Week 12.

2.6.1.3 PASI 50/ 75/ 90/ 100 and IGA mod 2011 0 or 1 response over time

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response at each visit up to Week 12, each secukinumab dose regimen will be compared to placebo using a logistic regression model with treatment group, baseline body weight, geographical region, and baseline PASI score as explanatory variables.

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response the placebo adjusted response rates including 95% confidence interval will be derived by visit up to Week 12. In addition, Fisher's exact test will be applied to pairwise treatment group comparisons to placebo.

Figures will be provided as well displaying estimates for responder rates by treatment including confidence intervals.

2.6.1.4 PASI score over time

Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group. Figures will also be provided.

2.6.1.5 IGA mod 2011 score over time

Summary statistics for the IGA mod 2011 score over time will be presented by visit and treatment group in contingency tables.

2.6.1.6 Time to PASI 75 response

Number and percentage of subjects with PASI 75 response based on the number of subjects in the FAS at risk as denominator will be provided by treatment group.

Between-treatment differences will be evaluated using a log-rank test, stratified by geographical region, presence of psoriatic arthritis, to compare the cumulative rates between secukinumab treatment groups versus placebo. The hazard ratios for the comparisons and 95% confidence intervals will be computed using a stratified cox proportional hazards regression model with treatment and baseline PASI as explanatory variable and stratified by geographical region, and baseline body weight.

Subjects without PASI 75 response will be considered as censored at Week 12.

[redacted]

2.6.1.9 Psoriatic arthritis

Summary statistics will be [redacted] provided for ACR 20 / 50 / 70 responses as well as for ACR component variables.

2.6.1.9.1 Definition of ACR 20/50/70 response and ACR Components

Evaluations to determine ACR response (ACR 20/50/70) include tender and swollen joint counts, HAQ-DI, PtGA Activity, PtGA Pain, PhGA PsA and acute phase reactant (ESR and hsCRP). The elements of the ACR scoring system are used in the same way as in standard trials of rheumatoid arthritis, with the exception of the number of joints tested, to include distal

interphalangeal joints of the feet and carpometacarpal joints of the hands, i.e., 78 joints for tenderness and 76 joints for swelling.

ACR 20/50/70

ACR 20, 50 or 70 responses correspond, respectively, to at least 20%, 50% or 70% improvement in comparison with baseline in the number of tender and swollen joint counts, in addition to similar improvements in at least three of five domains-HAQ-DI measure of disability, acute phase reactant (CRP or ESR) and the VAS scores of PtGA Activity, PtGA Pain and PhGA PsA.

ACR20 is a binary response variable defined for each subject. A subject will be considered a responder according to ACR20 criteria if he/she has at least (i.e., ≥):

- 20% improvement from baseline in tender 78-joint count
- 20% improvement from baseline in swollen 76-joint count
- 20% improvement from baseline in at least 3 of the following 5 measures:
  - Patient's assessment of PsA pain (VAS 100 mm)
  - Patient's global assessment of PsA disease activity (VAS 100 mm)
  - Physician's global assessment of PsA disease activity (VAS 100 mm)
  - Patient self-assessed disability (Health Assessment Questionnaire [HAQ©] score)
  - Acute phase reactant (C-reactive protein [hsCRP]) **or** Erythrocyte sedimentation rate (ESR).

In the definition above, the *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment.

Primarily, CRP will be used to calculate ACR response: ESR will only be used in the event CRP is missing.

ACR50 and ACR70 are defined in the same way as ACR20 by replacing the 20% with 50% and 70% improvement from baseline, respectively.

ACR Components

Tender 78 joint count and swollen 76 joint count

Joint counts will be performed at scheduled visits by the independent assessor(s) who must be well trained and part of the site personnel**.** Whenever possible, the same evaluator should perform these assessments at all visits.

The 78 joints assessed for tenderness include the 8 distal interphalangeal, 10 proximal interphalangeal and 10 metacarpophalangeal joints of the hands, the 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows , 2 shoulders , 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints plus 10 additional joints often involved in PsA (the first carpometcarpal and the DIP joints of the toes). All of these except for the hips are assessed for swelling. Joint tenderness and swelling to be graded present (1) or absent (0). Synovial fluid and/or soft tissue

swelling but not bony overgrowth represents a positive result for swollen joint count. Data is recorded for tender and swollen joints (right or left side), i.e. a box (no, yes or not applicable) needs to be ticked for all joints. In addition, the total number of tender and swollen joints (right and left) will be automatically calculated.

If the number of joints for which data were available (e.g., T) is less than 78/76 for the tender/swollen joint assessment, the number of tender/swollen joints (e.g., t) will be scaled up proportionately (i.e., 78*t/T or 76*t/T for tender or swollen joint count).

For the change in tender joint counts and swollen joint counts will be summarized.

Patient's assessment of PsA Pain

The patient's assessment of pain will be performed using 100 mm visual analog scale (VAS) ranging from "no pain" to "unbearable pain" after the question "*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your rheumatoid arthritis today*".

For the change in PsA pain, the changes from baseline will be summarized.

Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using 100 mm VAS ranging from "very good" to "very poor", after the question "*Considering all the ways rheumatoid arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today*".

The change in patient's global assessment from baseline will be summarized.

Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "*Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today?"* To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that subject.

The change in physician's global assessment from baseline will be summarized.

Erythrocyte sedimentation rate (ESR)

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits.

The change in ESR from baseline from baseline will be summarized.

High-sensitivity C-reactive protein (hsCRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Since the results of this test may unblind study personnel, results from the central lab will be provided for screening and baseline

only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

The change of hsCRP from baseline will only be summarized.

2.6.1.10 Relationship between response to secukinumab treatment and having failed to respond to previous biologic psoriasis therapy

Response variables PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 by visit will be tabulated versus previous systemic psoriasis therapy, by treatment group.

2.6.2 Secondary statistical model, and method of analysis

Not applicable.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data for ACR response variables will be handled as below.

1. Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through week 52.
2. Subjects who do not have the required data at baseline and at the specific time point to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) will be classified as non-responders.

For subjects who switch treatment after induction period, values of induction period are not carried forward to maintenance period.

Following the intent-to-treat principle for subjects who prematurely discontinue treatment, but who are observed in the follow-up period, efficacy data collected in follow-up periods will be linked to planned but missed study visits as well.

2.6.4 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-7.

Table 2-7 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Logistic regression	Summary statistics for continuous data	Time-to-event analysis	Graphs
PASI 75 response @ Week 12	X	X			X*
IGA 0/1 response @ Week 12	X	X			X*
PASI 90 response @ Week 12	X	X			X*
PASI 75 response @ Week 52 for PASI 75 responders at Week 12	X				
Loss of PASI 75 response for PASI 75 responders at Week 12				X	
IGA 0/1 response @ Week 52 for IGA 0/1 responders at Week 12	X				
Loss of IGA 0/1 response for IGA 0/1 responders at Week 12				X	
PASI 50/75/90/100 and IGA 0/1 response over time	X	X			X**

Variable(s)	Summary statistics for binary/ categorical data	Logistic regression	Summary statistics for continuous data	Time-to-event analysis	Graphs
Time to PASI 75 responders at Week 12				X	X
PASI score over time			X		X**
ACR 20/50/70 response in psoriatic arthritis subjects over time	X				X**
IGA mod 2011 categories over time	X				
[redacted]					

* dot plot; ** time course plot

2.7 Safety analyses

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

Treatment groups for evaluation

The summaries of evaluation will be reported for both induction period and entire study period. The following groups will be used:

- for induction period:
  - Secukinumab 150mg, Secukinumab 300mg, Placebo;
- for entire study period:
  - Secukinumab 150mg, Secukinumab 300mg, Placebo,
    Any Secukinumab 300mg, Any Secukinumab dose.

Safety analyses will be performed on treatment received or actual treatment (See Section 5.4.2, Safety Set).

2.7.1 Adverse events (AEs)

For adverse events and other binary safety variables crude incidence and exposure time-adjusted incidence will be derived as described below and summarized in Table 2-8.

All adverse events are summarized based on treatment emergent only. The definition for "treatment emergent" is as below:

- events started after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term
- and started prior to the last dose plus 84 days (inclusive)

All adverse events will be listed with "treatment emergent" flag displayed.

Table 2-8 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP/RMP risks (special AE interest)	SAEs	AEs-SMQ	AEs by severity	study treatment related AEs, death & other significant AEs	notables (lab/vitals)
treatment period (up to week 12)	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence	•crude incidence
treatment period (including all data)	•crude incidence •exp.time adjusted incidence*	•crude incidence •exp.time adjusted incidence*	•crude incidence •exp.time adjusted incidence*	•crude incidence	•crude incidence	•crude incidence

*Note, Exposure adjusted incidence rates will be provided and follow the guideline as below:

- Primary SOC level for AE and SAE
- Level 1 for risks and SMQ
- PT level for SAE
- PT level for AE ≥ 2% or incidence rate per 100 subject years ≥ 5.0 in AIN457 300 mg or AIN457 150 mg treatment group
- Other selected AEs of special interest on lower levels (e.g. PT or SMQ level 2), if appropriate

The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.4.6. In addition, exposure time-adjusted incidence rates will be provided for the treatment period including all data (see Section 5.4.7).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

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

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

A graphical display of the crude rates or exposure adjusted incidence rates within system organ classes will be presented as follows: For all AEs regardless of severity and seriousness, the point estimate within system organ classes will be presented graphically with system organ class on the y-axis. This figure will consist of two panels: i) point estimate of AEs, ii) point estimate of serious AEs. For the exposure adjusted incidences a linear-scale will be used on the x-axes.

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

Algorithms for date imputations will be provided in Section 5.

For SAEs occurred during screening a listing will be prepared for all subjects screened including screening failures.

The adverse events occurred after the treatment errors in those subjects who received erroneously the wrong treatment at least once, will be listed.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than X% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

A listing of significant adverse event will be provided for China only per China Health Authority. The significant adverse event is defined as marked hematological and other laboratory abnormalities and any adverse events, apart from serious adverse events, that led to an intervention, including withdrawal of drug treatment ordose reduction.

2.7.1.1 Adverse events of special interest / grouping of AEs

Exposure adjusted incidence rates for adverse events of special interest will be provided as in Table 2-9.

Table 2-9 Table of AEs of special interest

Special AE interest:	Notes (All levels are displayed)
Inflammatory bowel disease (NMQ) (narrow)	Include Crohns (PT) and Ulcerative colitis (PT) and others
Opportunistic infections (NMQ)	
Candida infections (HLT)	
Herpes viral infections (HLT)	Both Oral and other are included
Staphylococcal infections (HLT)	
MACE (MI, Stroke, Cardiovascular death) (NMQ)	
Malignant or unspecified tumours (SMQ)	Including BCC, SCC in SMQ
Malignant or unspecified tumours (SMQ excl BCC and SCC) (NMQ)	
Upper respiratory tract infections (HLT)	

Other safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in GPS at the path [/vob/util/sasviews/tms].

Crude rate of important identified and potential risks from Case Retrieval Sheet will be provided for all (non-serious and serious) cases and for all serious cases. Exposure-time adjusted rates will be provided for treatment period including all data for all (non-serious and serious) cases and for all serious cases. In addition, listings will be provided for the related AE risks.

Risk measures and confidence intervals will be derived according to Section 5.

The version of the Case Retrieval Sheet used for the analyses will be described in a footnote. This includes MedDRA version and Novartis MedDRA Query (NMQ) dictionary date.

Important note: For the evaluation of risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

2.7.2 Deaths

Separate summary and listing will be provided for deaths.

2.7.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry).

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

change from baseline = post baseline value – baseline value

Only “on-treatment” laboratory data will be summarized (i.e. assessments within last dose plus 84 days). All laboratory data will be listed with “on-treatment” flag displayed. If two measurements are taken on the same date/time/CRF visit then use the average of two assessments.

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-10: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP).

The number and percentage of subjects with CTCAE grade newly occurring or worsening after baseline will be presented. These summaries will be split into hematology and chemistry.

Table 2-10 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. If no pre-treatment value exists, also a value recorded after first dose can be used as baseline if it was collected on the same day as first dose, see Section 2.1.1.3.

Exposure time adjusted incidence for subjects with newly occurring neutropenia of CTCAE grade >=2 will be summarized and listed in the listing.

The number and percentage of subjects with newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-11.

Table 2-11 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN ALT or AST >3xULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))
TBL	>1xULN;>1.5xULN; >2xULN; >3xULN,
ALP	>1.5xULN;>2xULN; >3xULN; >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >1.5xULN; ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN; ALT or AST >20xULN & TBL >2xULN;
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP >2xULN may not result in severe DILI. ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**) or reported Hy's Law case Note: "Hy's Law case" is a lower level term in MedDRA (10070546) and may be reported as AE.

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g., a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5xULN.

Individual subject data listings will be provided for subjects with newly occurring or worsening abnormal laboratory data. Data of subjects with newly occurring liver enzyme abnormalities will be listed in an additional listing.

Fasting laboratory tests including fasting plasma glucose and fasting lipids will be evaluated only at screening. No analysis will be done for these measurements.

For urinalysis, standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood (non-hemolyzed), urine blood (hemolyzed), bilirubin, ketones, WBC will be done at screening. For urinalysis, frequency tables will be presented.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Fridericia (QTcF) corrections will be presented for QTc. QTcF will be derived by the programmer using the formula: QTcF = QT/CubeRootRR(seconds).

QTc will be summarized by computing the number and percentage of subjects with:

- QTc > 500 msec
- QTc > 480 msec
- QTc > 450 msec
- QTc changes from baseline > 30 msec
- QTc changes from baseline > 60 msec
- Sinus pause > 3 sec, if appropriate
- PR > 250 msec

Summary statistics will be presented for ECG variables by visit and treatment group.

A listing of all newly occurring or worsening abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

2.7.4.2 Vital signs

Systolic and diastolic blood pressure are measured twice at each scheduled visits, and two mesurments are entered on the CRF page in this study. The average value of the two mesurments will be used in the vital sign analysis.

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

Only “on-treatment” vital signs will be summarized (i.e. assessments within last dose plus 84 days). All vital signs will be listed with “on-treatment” flag displayed.

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-12 below. A listing of subjects with newly occurring notably abnormal vital signs will be provided.

Table 2-12 Criteria for notable vital sign abnormalities

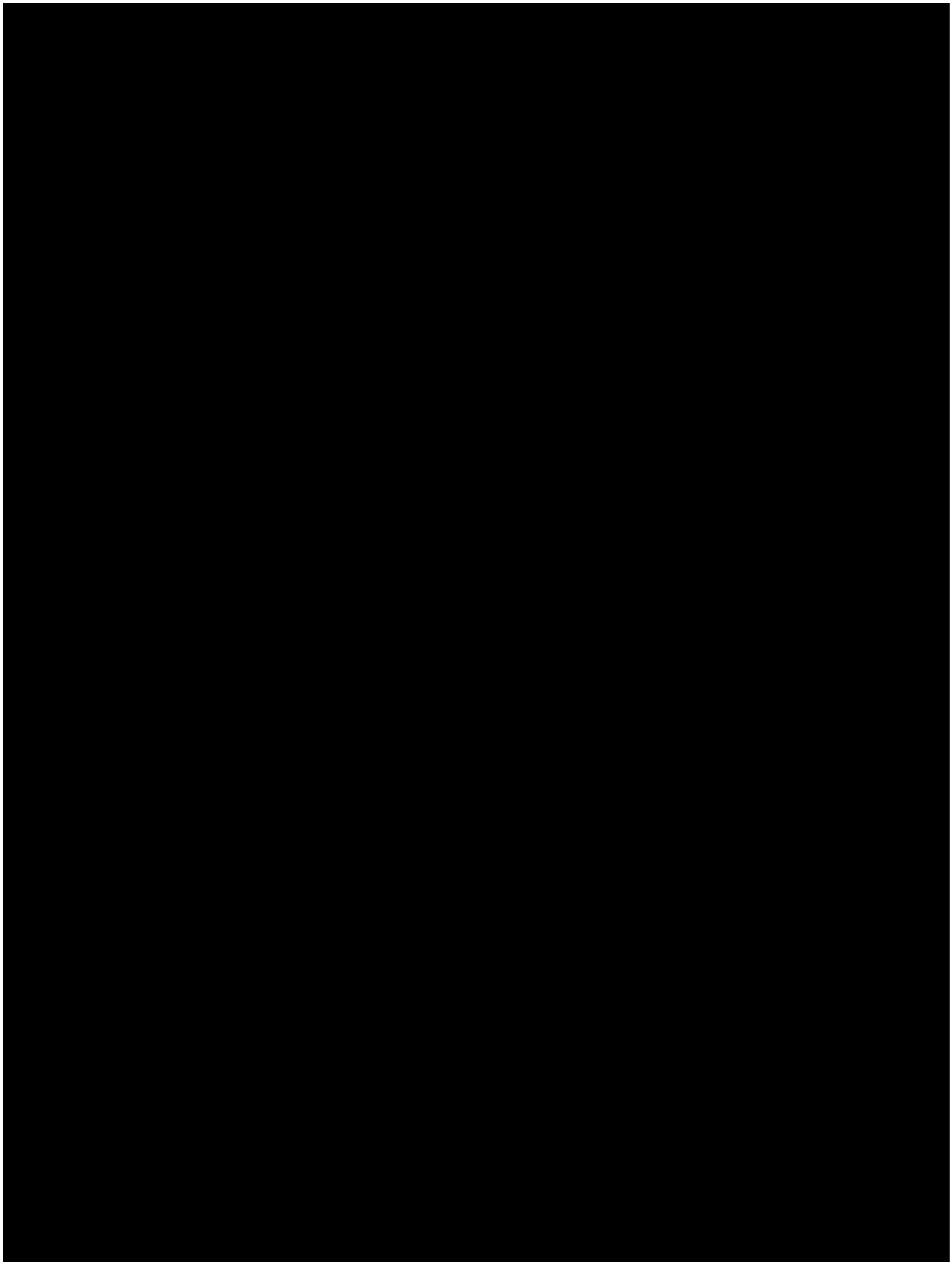
Vital sign (unit)	Notable abnormalities
Systolic blood pressure (mmHg)	>= 140 mmHg or < 90 mmHg
Diastolic blood pressure (mmHg)	>=90 mmHg or <60 mmHg
Pulse (bpm)	> 100 bpm or <60 bpm

[redacted]

2.10 Patient-reported outcomes

Three tools will be used in this study:

[redacted]



2.10.2 Health Assessment Questionnaire- Disability Index (HAQ-DI) (subjects with PsA only)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ (Health Assessment Questionnaire© – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 items in eight categories of functioning including dressing & grooming, arising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (without any difficulty [0]), with some difficulty (1), with much difficulty (2), and unable to do (3). The HAQ-DI also includes questions about the use of 'aids or devices' and aid from other people to supplement the answers given to the 20 items.

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7

- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if any "aids or devices" and/or "help from another person" items at the bottom of each page are checked with the exception of “other”, the category to which they apply will be adjusted upward to "2". If the basic score is already "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can only change a category's score to "2"; they do not change the score to a "1" or a "3". Companion aids/devices items for HAQ-DI categories are presented in Table 2-13. No score will be adjusted for “other” ticked, regardless of the “other” specification.

The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. If fewer than 2 of the categories are missing, divide the sum of the categories by the number of answered categories. The higher score indicates greater disability.

[redacted]

Table 2-1 Companion aids/devices items for HAQ-DI categories

HAQ-DI Category	Companion Item
Dressing & Grooming	Devices used for dressing (button hook, zipper pull, long handled shoe horn etc.)
Arising	Built up or special chair
Eating	Built up or special utensils
Walking	Cane walker, crutches
Hygiene	Raised toilet seat, bathtub seat, bathtub bar Long handled appliances in bathroom
Reach	Long handled appliances for reach
Grip	Jar opener (for jars previously opened)

The purpose of the HAQ-DI in this study is to assess the functional ability of subjects with PsA.

[redacted]

2.10.3 Patient's global assessments (subjects with PsA only)

When a subject has PsA at randomization defined as at least 3 points of the CASPAR criteria and at least 3 tender and 3 swollen joints at randomization, the subject will be asked to complete the following non-validated instruments using using 100 mm VAS ranging from "very good" to "very poor" on the VAS:

- Patient's Global Assessment of disease activity (PtGA Activity)
- Patient's Global Assessment of psoriatic arthritis pain (PtGA Pain)

Standard summary statistics will be shown for the PtGA activity and PtGA pain assessment.

2.10.4 Handling of missing values/censoring/discontinuations

For [redacted] HAQ-DI scores, missing values will be replaced by LOCF. Baseline values will not be carried forward. If no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose. In addition, missing baseline (PROs) values will be replaced by the means or modes of non-missing baseline values stratified by age group (<65 years, 65 years and older) and gender, for continuous scale or categorical/ordinal scale, respectively.

2.11 Biomarkers

Not applicable.

2.12 Other Exploratory analyses

Not applicable.

2.13 DMC

Only safety data will be reviewed by the DMC, the detailed table/listing/figure (TFL) list will be provided in an excel file.

There will be two sets of TLFs produced. The first set will be the Blinded Set which will use the dummy treatment group in the TFLs. However the study data are real. This set of TLFs will be made available to the Novartis Blinded team apart from the DMC members. The second set will be the unblinded set. This will include real study data which will be assigned to the treatment groups based on the randomization. This means that the treatment assignment in these TLFs will be real. This set of TLFs will only be handled by the Unblinded Team (Independent statistician, independent programmer) and will only be shared with DMC members.

2.14 Interim analysis

After last patient completed the week 16, an analysis will be conducted [redacted]. At Week 16 analysis, the primary endpoint analysis at Week 12 together with the Week 16 efficacy data analysis will be performed. For safety analysis, the data till week 16 will be analyzed.

3 Sample size calculation

This global study aims at complementing the safety and efficacy knowledge on secukinumab with data obtained from patients in China and other countries. The planned cohort sizes address this objective, in particular with respect to safety data.

At Baseline, subjects will be randomized to one of the two secukinumab treatment regimens or to placebo in a 2:1:1 ratio (300mg Secukinumab: 150mg Secukinumab: placebo). After the first 12 weeks of treatment, non-responders under placebo will be re-assigned to 300 mg secukinumab treatment regimen.

Reported PASI 75 response rate to placebo is generally in the range of 3% to 7% (Papp 2006; Menter 2008; Leonardi 2008; Papp 2008) whilst in a recent phase III trial, observed PASI 75 response rate to placebo in Chinese subjects after twelve weeks of treatment was above 11% ("Safety and effectiveness of ustekinumab/stelara in Chinese patients with psoriasis", ClinicalTrials.gov Identifier: NCT01008995). It is estimated that in the present study, up to 10% of the subjects under placebo will achieve a PASI 75 response during the first twelve weeks of treatment (induction period).

According to CFDA requirement in use of biologic drug, it is planned to randomize 536 subjects at Baseline, i.e., using a 2:1:1 ratio, 268 patients for 300 mg secukinumab regimen and 134 patients for 150 mg secukinumab regimen and placebo group, respectively.

The PASI 75 and IGA mod 2011 0 or 1 response rates of secukinumab regimens at Week 12 are assessed based on Phase III trials. PASI 75 response rates at Week 12 are approximately 79.4% (95% C.I: [76.2, 82.4]) for the 300 mg secukinumab regimen and 69.2% (95% C.I: [65.6, 72.6]) for the 150 mg secukinumab regimen. IGA mod 2011 0 or 1 response rates at Week 12 are approximately 65.0% (95% C.I: [61.3, 68.6]) for the 300 mg secukinumab regimen and 51.4% (95% C.I: [47.7, 55.2]) for the 150 mg secukinumab regimen. Since two secukinumab dose regimens will be tested in parallel versus placebo with respect to the co-primary endpoints, PASI 75 response and IGA mod 2011 0 or 1 response after 12 weeks of treatment, the type-I-error for each comparison will be split to $\alpha/2$ (family-wise α=2.5%, one-sided). With 536 (using a 2:1:1 ratio) subjects and assuming a response rate in the placebo group of 10% for PASI 75 response and IGA mod 2011 0 or 1 response, the power to demonstrate a response rate of 65.6% for PASI 75 and 47.7% for IGA mod 2011 0 or 1 in the secukinumab groups is above 99%, based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions).

The PASI 90 response rates of secukinumab regimens are approximately 56.6% (95% C.I: [52.8, 60.3]) for the 300 mg secukinumab regimen and 41.1% (95% C.I: [37.4, 44.9]) for the 150 mg secukinumab regimen.

With respect to the secondary endpoint of PASI 90 response at week 12 and with sample size of 536 (using a 2:1:1 ratio), the power to detect differences in response rates for each secukinumab dose regimen versus placebo is above 99%, based on Fisher's exact test with type-I-error of $\alpha/2$ (family-wise α=2.5%, one-sided) for each comparison and placebo response rate of 5%.

4 Change to protocol specified analyses

Due to a very small number of subjects with relapse are expected, the Kaplan Meier analysis for time to relapse will not be provided.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

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

5.1.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 31DECYYYY, date of death).

2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death).

3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

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

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

2. Else AE start reference date = treatment start date

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

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

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

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

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

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

b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

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

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

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

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

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

5.1.3 Concomitant medication date imputation

Impute CM end date:

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

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

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

Impute CM start date:

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

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

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

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

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

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

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

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

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

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

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

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

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.4 First diagnosis date (Pso, PsA) imputation

1. If first diagnosis date is complete then imputed first diagnosis date = first diagnosis date.

2. If only year is present in the first diagnosis date then do the following:

a. If the year part of the first diagnosis date is equal to the year part of the inform consent date then imputed first diagnosis date = Jan 1 of the year of the first diagnosis date

b. Otherwise imputed first diagnosis date = Jul 1 of the year of the first diagnosis date

3. If only month and year part are present in the first diagnosis date then do the following:

a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date then imputed first diagnosis date = 1st of the month of the year of the first diagnosis date

b. Otherwise imputed first diagnosis date = 15th of the month of the year of the first diagnosis date

5.1.5 Other imputations

Only PASI and IGA mod 2011 based response variables are imputed with multiple imputation or non-response, other response variables [redacted] will be imputed with LOCF.

For [redacted] HAQ-DI scores, missing values will be replaced by LOCF. Baseline values will not be carried forward. If no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose. In addition, missing

baseline (PROs) values will be replaced by the means or modes of non-missing baseline values stratified by age group (<65 years, 65 years and older) and gender, for continuous scale or categorical/ordinal scale, respectively.

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

5.2 AEs coding/grading

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

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

5.3 Laboratory parameters derivations

See Section 2.7.3.

5.4 Statistical models

5.4.1 Analysis of continuous data

5.4.1.1 Summary statistics

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group. For PASI score, DLQI total scores, summary statistics will be derived for absolute and percentage changes from baseline.

5.4.2 Analysis of binary (and categorical) data

5.4.2.1 Summary statistics

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With z as (1-alpha/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$

Then the lower limit is for $p > 0, \left(L = 0 \text{ for } p = 0\right)$,

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is for $p < 1, (U = 1 \text{ for } p = 1),$

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

For response variables (e.g. for IGA mod 2011 0 or 1, PASI 75, PASI 50, PASI 90 and PASI 100 response) the placebo adjusted response rates (risk difference) including 95% confidence interval will be derived by visit.

Figures will be provided for PASI 75 response (upper left) PASI 90 response (upper right), PASI 100 response (lower left) and IGA mod 2011 0 or 1 response (lower right) at Week 12 and Week 16 as dot plots displaying treatments on the x-axis and point estimates including 95% confidence intervals on the y-axis.

For time courses of response variables, the point estimate at each time point including 95% confidence interval will be plotted.

5.4.2.2 Logistic regression

Binary outcome variables, including PASI 50 / 75 / 90 / 100 response and IGA mod 2011 0 or 1 response, will be evaluated using a logistic regression model with treatment regimen, body weight category, geographical region and baseline PASI score. Odds ratios will be computed for comparisons of secukinumab versus placebo utilizing the logistic regression model fitted.

If response rates are 0% or 100% in one of the treatment groups, fisher's exact test will be used for the comparison, and odds ratio estimate will not be displayed in outputs, but "-" will be shown.

The odds ratio will be calculated such that an odds ratio >1 is favorable for secukinumab. Using PROC GENMOD to calculate the confidence interval for the odds ratios assumes asymptotic normality of the Wald estimate for the regression coefficient. The 95% confidence interval for the regression parameter of the active treatment effect relative to control(s) will be calculated using an exponential transformation to create the confidence interval for the odds ratio.

All p-values reported on linear hypotheses about regression coefficients will be based on the Wald tests from Type III analyses. In the SAS procedure PROC GENMOD, a Type III analysis will be performed by adding the model options: TYPE3, DIST=BIN, and LINK=LOGIT. If logistic regression model does not converge, an exact logistic regression will be applied to response variables at each visit, and the following steps will be performed:

1. Run the PROC GENMOD procedure with EXACT statement;
2. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with removing continous variable (i.e., baseline PASI) and followed by categrical varable (geographical region, body weight category);

3. If convergence not reached, perform Fisher's exact test.

It should be noted that this model might not converge if response rates are too low.

For subgroup analyses of PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response, the logistic regression model will be fitted with treatment group, body weight category, geographical region and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab versus placebo utilizing the logistic regression model fitted. In case of non-convergence, Fisher's exact test will be performed.

Of note, for the subgroup analysis by body weight category (region), the weight category (region) variable will not be fitted in the logistic regression model.

5.4.3 Multiple imputations for response variables

Primary and secondary endpoints will be evaluated by Logistic regression and odds ratio estimate as described in the primary analysis method with multiple imputations for missing values. In addition, logistic regression analysis for PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visits will be analyzed using multiple imputation method.

In the multiple imputations analysis the response status will be imputed based on the individual treatment arm information.

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty.

Missing values for the 'change from baseline PASI score' and 'IGA mod 2011 score' will be imputed simultaneously based on an underlying joint normal distribution and using a Markov Chain Monte Carlo (MCMC) method. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score. Assuming normality for the 'IGA mod 2011 score' is motivated by Schaefer (1997), where it was shown that the multivariate normal approximation for the imputation of incomplete categorical and binary data is robust.

The imputations will be done separately for each treatment group including baseline weight, region (China/non-China), failure to at least one previous biologic (yes/no), and number of previous systemic therapies as additional covariates.

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables with multiple imputations method.

The number of imputations will be set to 100, the seed for the random function will be set to 4572318 for this study. To generate the multiple imputed data sets, the SAS procedure MI can be used as follows:

The input data set <pasi_iga> should have one record per subject with baseline PASI score and IGA mod 2011 score as well as all changes from baseline PASI and post-baseline IGA mod 2011 score.

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi_iga> OUT=<impdata> SEED=457<studycode> NIMPUTE=100;
 VAR <baseline weight>  <region> <failure to at least one biologic>
     <number of previous systemic therapies>
     <baseline PASI> <baseline IGA>
     <change from baseline PASI week 1> - <change from baseline PASI week primary endpoint>
     <IGA week1> - <IGA week primary endpoint>;
  BY <treatment group>;
RUN;
ODS LISTING;
```

Programming notes:

- The SAS procedure MIANALYZE expects a variable called "_IMPUTATION_ which is generated by the MI procedure. It might be needed to set the SAS option "VALIDVARNAME=UPCASE" temporarily in the program before the MI call, this option should be reset after the MIANALYZE call to VALIDVARNAME=V6.
- In case there are no missings in one treatment group, the MI procedure does not impute any values. In this case the corresponding data need to be imputed manually outside PROC MI and added to the dataset <impdata>.

The imputed data are saved in data set <impdata>. The outcomes of interest, i.e. the PASI 50/75/90/100 response and IGA mod 2011 0 or 1 response will be calculated, e.g. as follows:

```
DATA <impdata2>;
 SET <impdata>;
IF <change from baseline PASI week primary endpoint>/<baseline PASI>=0.90 THEN <PASI 90 response> =1;
ELSE <PASI 90 response>=0;
<…repeat for all PASI response…>

IF <baseline IGA> >=3 THEN DO;
          IF <IGA week primary endpoint> < 1.5 THEN <IGA 0/1 response> =1;
     ELSE IF <IGA week primary endpoint> >=1.5 THEN <IGA 0/1 response> =0;
     ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE IF <baseline IGA>=2 THEN DO;
          IF <IGA week primary endpoint> < 0.5 THEN <IGA 0/1 response> =1;
     ELSE IF <IGA week primary endpoint> >=0.5 THEN <IGA 0/1 response> =0;
     ELSE PUT "E" "RROR:" stysid1a=;
END;
ELSE <IGA 0/1 response> =0;
RUN;
```

The treatment differences for each imputed data set will then be evaluated by Logistic regression and ODDS ratio as described in Section 5.4.5.3. This analysis will be done by _IMPUTATION_ for the comparison to the placebo treatment group. The model should be estimating response probability = 1 by using DESECENDING option. Using the ESTIMATE option in the GENMOD procedure and the ODS OUTPUT data set "Estimates" provides the estimate for the odds ratio and confidence intervals.

```
PROC GENMOD <option>;
CLASS <stratum> <treatment>;
MODEL <response> = <explanatory variables> / link=logit dist=bin type3;
BY <by-variables);
ESTIMATE “OR. AIN 300 mg VS. Placebo” <treatment> 1 -1/exp;
ODS OUTPUT Estimates=Estimates;
RUN;
```

The MIANALYZE procedure expects the parameter estimate in the variables ESTIMATE, and the corresponding standard error in the variable STDERR. Measurements can be obtained from “Estimates” dataset by selecting the row with ODDS ratio estimates.

```
Data <modified dataset>;
  set Estimates;
  if substr(label,1,3)= “Exp”;
  ESTIMATE=LBetaEstimate;
  STDERR=StdErr;
  effect= “OR”;
  if missing(ESTIMATE) or missing(STDERR) then delete;
RUN;
```

The estimates and standard errors based on the 100 imputed data are then combined by applying Rubin’s rules for multiple imputed data sets, see Little and Rubin (2002).

Programming notes:

- The variables ESTIMATE and STDERR in the input data set for the MIANALYZE procedure may not be missing. Records with missing values need to be deleted and the variable _IMPUTATION_ needs to be renumbered and regenerated since for each by-group the procedure expects consecutive numbers starting at 1.
- The ESTIMATE and STDERR in terms of odds ratios from logistic regressions will be transformed to follow a normal distribution before MIANALYZE procedure. They will be transformed back to Odds Ratio to get the corrected ESTIMATE and corresponding CIs.

The SAS procedure MIANALYZE will be applied as follows:

Step 1:

```
DATA <modified dataset_t>;
     SET <modified dataset>;
     estimate=log(ESTIMATE);
     stderr=(log(LBETAUPPERCL)-log(LBETALOWERCL))/(2*1.96);
RUN ;

ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=<results> VarianceInfo=<varinfo> ModelInfo=<modelinfo>;
PROC MIANALYZE PARMS=<modified dataset>;
  BY <by-variables>;
  MODELEFFECTS OR;
RUN;
ODS LISTING;

data <results_back>;
```

```
    set <results>;
    estimate=exp(ESTIMATE);
    LCLMEAN=estimate*exp(-1.96*stderr);
    UCLMEAN=estimate*exp(+1.96*stderr);
RUN ;
```

5.4.4 Analysis of time-to-event data

Number and percentage of subjects with a clinical event based on the number of subjects in the analysis set at risk as denominator will be provided by treatment group.

Median time to event (i.e., loss of PASI 75, IGA 0/1 response) and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation (PROC LIFETEST option conftype=log-log). In addition, for pre-specified time intervals the following will be presented in an output:

- for each treatment group and time interval: subjects at risk, subjects with event, subjects with event divided by subjects at risk, cumulative subjects with event and cumulative event probability including 95% confidence interval

The pre-specified time intervals for different treatment periods are as follows:

Treatment period: “0 to ≤4 weeks”, “>4 weeks to <=8 weeks”, “>8 weeks to <=12 weeks”, “>12 weeks to <=16 weeks”, “>16 weeks to <=20 weeks”, “>20 weeks to <=24 weeks”, “>24 weeks to <=28 weeks”, “>28 weeks to <=32 weeks”, “>32 weeks to <=36 weeks”, “>36 weeks to <=40 weeks”, and “>40 weeks”.

For the statistical appendix, the subjects identifier, the time to event, the number of subjects with an event, number of subjects remaining at risk in the treatment group in the analysis set, estimate of the event rate and its estimated standard error, as estimable, will be provided for each treatment group using the SAS procedure LIFETEST.

Subjects at risk, timepoint “0” and censoring will be defined as described in Table 5-1 below:

Table 5-1 Time to event: definition of risk set, timing and censoring by variable

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed	Informative censoring
Loss of PASI 75	All PASI 75 responders at Week 12 per analysis visit AND at least have one PASI assessments after Week 12	Week 12 per analysis visit	Date of 1st visit with loss of PASI 75 observed	End of treatment period as per CRF disposition page	Censor (if ConMed taken before the event)	Study phase discontinu-ation with reason “lack of efficacy”

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed	Informative censoring
Loss of IGA 0/1	All IGA 0/1 responders at Week 12 per analysis visit AND at least have one IGA assessments after Week 12	Week 12 per analysis visit	Date of 1st visit with loss of IGA 0/1 observed	End of treatment period as per CRF disposition page	Censor (if ConMed taken before the event)	Study phase discontinu-ation with reason "lack of efficacy"

Psoriasis ConMed is define in MAP appendix

Time-to-event will be derived as:

- date of event minus date of time=0 plus 1 day for subjects experiencing the event or
- date of censoring minus date of time=0 plus 1 day for subjects not experiencing the event

5.4.5 Crude incidence and related risk estimates

5.4.5.1 Crude incidence and 100*(1-α)% confidence interval

For n subjects, each at risk to experience a certain event with probability π, the crude incidence is estimated as p=x/n, where x is the number of subjects with the event.

Absolute and relative frequencies will be displayed as well as 95% confidence interval for the relative frequency based on the score method including continuity correction (Newcombe 1998).

With $_z$ as (1-α/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), $_n$ as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / $_n$) it is $q = 1 - p$.

Then the lower limit is

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right).$$

Note: if p = 0 then L = 0 and if p = 1 then U = 1.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

5.4.5.2 Relative risk and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g., placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the relative risk is estimated as p_1/p_0 with $p_1=x_1/n_1$ and $p_0=x_0/n_0$.

An asymptotic 100*(1-α)% confidence interval on the relative risk will be based on the back-transformed large sample confidence limits on the log-transformed relative risk estimate which are obtained by application of the delta-method and Slutzky's theorem (Lachin 2000). The SAS procedure PROC FREQ with option RELRISK in the TABLES statement will be used to provide the asymptotic 100*(1-α)% confidence interval on the relative risk. The estimate is not computed if either x_1 or x_0 equals 0. In this case, or if the crude incidences are low in both groups, the relative risk will be approximated by the odds ratio for which an exact confidence interval will be obtained as specified in Section 5.4.5.3. If the relative risk is not well approximated by the odds ratio but asymptotic normality is questionable, STATXACT will be used.

5.4.5.3 Odds ratio and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g. placebo) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ with $p_1= x_1/n_1$ and $p_0=x_0/n_0$. A conditional exact 100*(1-α)% confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR.

5.4.5.4 Risk difference and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g., placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event, the risk difference is estimated as p_1-p_0 with $p_1= x_1/n_1$ and $p_0=x_0/n_0$.

Exact unconditional confidence limits for the risk difference will be obtained with SAS procedure PROC FREQ and option RISKDIFF in the TABLES statement, specifying the RISKDIFF option also in the EXACT statement.

5.4.6 Exposure adjusted incidence rate and related risk estimates

5.4.6.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or last dose plus 84 days whichever occur earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event.

Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

5.4.6.2 Exposure-adjusted event rate and 100*(1-α)% confidence interval

For each of n subjects t_j (j=1,...,n) specifies the exposure time. The number of occurrences of an treatment emergent event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of events (episodes). Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

Lower confidence limit $L = \frac{0.5c_{\alpha/2,2D}}{T}$ for D>0, 0 otherwise,

Upper confidence limit $U = \frac{0.5c_{1-\alpha/2,2D+2}}{T}$

where $c_{\alpha,k}$ is the α th quantile of the Chi-square distribution with k degrees of freedom.

5.5 Rule of exclusion criteria of analysis sets

Protocol deviations for exclusion from analysis sets are defined in Table 5-2.

Table 5-2 Subject classification rules

Analysis set	PD Categories Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
Randomization set	NA	Misrandomized subject
FAS (Full Analysis Set)	DVSPID: INCL02; OTH17	Misrandomized subject
Safety	DVSPID: INCL02; OTH17	Subjects who did not take any study treatment

INCL02: ICF missing or not signed prior to initiating study procedure

OTH17: Severe ICH-GCP non-compliance of study site

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