NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457A2326 / NCT02826603

A 52-week, multicenter, randomized, double-blind study of secukinumab (300 mg) to demonstrate efficacy as assessed by Psoriasis Area and Severity Index and Investigator's Global Assessment after 12 weeks of treatment, compared to ustekinumab, and to assess long-term safety, tolerability and efficacy in subjects with moderate to severe plaque psoriasis (CLARITY)

Statistical Analysis Plan (SAP)

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9-Nov-2017	Prior to PEA	Creation Amendement 1.0 version		• Change to present one-sided p-values instead of two-sided p-values. • Update visit window derivation [redacted] • Update the subgroup analysis [redacted]. • Update Section 2.4.1.2 Multiple assessments within visit windows • Update Section 2.5.3 Handling of missing values/censoring/discontinuations: add pure NRI method • [redacted] • Drop figure for adverse events. • Modify liver events definition.
10-Apr-2018	Prior to final analysis	Creation Amendment 2.0 version	•	• Update wording 'Previous Non-biologic systemic Therapy'. • Update RAP M7.1 and M7.2 to TFL shell and RAP M8 to PDS. • Update Table 2-9 per eCRS. • Update typo on "ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Potential Hy's Law)". • For time to event analysis, add treatment comparison and update treatment interval. • [redacted] • Drop some of the safety analysis • Drop subgroup analysis other than weight •

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body surface area
CHMP	Committee for medicinal products for human use
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report/record form
FAS	Full analysis set
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase
HGB	Hemoglobin
IGA	Investigator's global assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IRT	Interactive response technology
LLN	Lower Limit of Normal
MACE	Major Adverse Cardiovascular Event
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PD	Protocol deviation
PT	Preferred Term
RMP	Risk Management Plan
SAS	Statistical analysis software
SAE	Serious adverse event
SPP	Safety Profiling Plan
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White blood cell

1 Introduction

Data will be analyzed by Novartis according to the data analysis section (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 CAIN457A2326 (CLARITY) study with reference to the study protocol amendment 1 and the project standard analysis plans [redacted]

1.1 Study design

This is a multicenter, randomized, double-blind, active-controlled, parallel-group trial in approximately 1100 subjects with moderate to severe chronic plaque-type psoriasis.

Randomization will be stratified by body weight collected at baseline, ≤ 100 kg (220 LB) or > 100 kg (220 LB). Subjects will be randomized using a 1:1 ratio into one of the treatment groups below:

- **Secukinumab arm**: will receive a dose of secukinumab 300 mg, which consist of two injections of the 150 mg pre-filled syringes;
- **Ustekinumab arm**:
  - Subjects weighing > 100 kg (220 LB) at baseline will receive a dose of 90 mg ustekinumab which consists of two injections of 45 mg pre-filled syringes;
  - Subjects weighing ≤ 100 kg (220 LB) at baseline will receive a dose of 45 mg ustekinumab which consist of one injection of the 45 mg pre-filled syringe + one secukinumab placebo

In addition, in order to maintain the blind, placebo injections matching secukinumab 150 mg pre-filled syringes will be given to subjects in ustekinumab arm.

The following study periods will be considered for analysis:

- **Screening period** (before Randomization)
- **Treatment period** (Randomization to Week 52, last dose at Week 48), including follow-up period (F4 and F8 visits) for prematurely discontinued subjects

Of note: data from follow-up period (i.e., treatment free follow-up period after EOT visit, which includes F4 and F8 visits) for prematurely discontinued subjects will be included in the analysis of treatment period.

The primary analysis will be performed at the time of Week 16 interim DBL. Treatment period up to Week 16 will be presented for the W16 interim analysis and all data will be presented for the final analysis.

1.2 Study objectives and endpoints

The primary objective of this study is to confirm the superiority of secukinumab versus ustekinumab with respect to PASI 90 and IGA mod 2011 0 or 1 response rates at Week 12 in treatment of moderate to severe plaque psoriasis.

The secondary objectives are to demonstrate the superiority of secukinumab versus ustekinumab with respect to:

- PASI 75 response at Week 12
- PASI 75 response at Week 4
- PASI 90 response at Week 16
- PASI 100 at Week 16
- IGA mod 2011 0/1 at Week 16
- PASI 100 at Week 12
- PASI 75 at Week 16
- PASI 90 at Week 52

Furthermore, additional aspects of long-term efficacy, safety and tolerability of secukinumab versus ustekinumab over a period of 52 weeks will be investigated.

Table 1-1 Primary, secondary [redacted] variables

Variable	Type
PASI 90 response at Week 12 (compared to Ustekinumab)	primary
IGA 0/1 response at Week 12 (compared to Ustekinumab)	primary
PASI 75 response at Week 12	secondary
PASI 75 response at Week 4	secondary
PASI 90 response at Week 16	secondary
PASI 100 response at Week 16	secondary
IGA 0/1 response at Week 16	secondary
PASI 100 response at Week 12	secondary
PASI 75 response at Week 16	secondary
PASI 90 response at Week 52	secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Novartis will be performing both a Week 16 interim analysis and final analysis (Week 52). Statistical software SAS version 9.4 or later will be used.

Data up to Week 16 will be presented for the Week 16 interim analysis and all data will be presented in the final analysis.

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 as one-sided for hypothsis testings and as two-sided for other analysis. Two-sided 95% confidence intervals will be displayed. If not otherwise specified, hypothesis testings will be based on one-sided p-values that the treatment effect is in favor of Secukinumab. The level of significance will be set to 2.5% (one-sided, family-wise type-I-error). 95% confidence intervals will not be used for decision making; they will only be used for estimation and will therefore always be two-sided.

All listings will be presented by treatment sequence.

Footnotes on outputs will be kept to a minimum also for outputs not covered in [redacted]

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
- Control treatment
  - Secukinumab placebo, 1 ml liquid formulation in a pre-filled syringe
  - Ustekinumab 45 mg, 0.5 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 [PDS].

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

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

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). If a subject discontinued early, then the last dose + 84 days or the last visit during the follow-up period whichever occurs earlier is considered.

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

2.2 Analysis sets

The following analysis sets will be used for the 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.

2.2.1 Subgroup of interest

The co-primary endpoints and secondary endpoints will be evaluated using the subgroups defined in Table 2-1. Subgroup analyses for the study endpoints are represented in Table 2-2.

Table 2-1 Subgroup definitions

Subgroup variables	Categories	Description	Label for outputs	Suffix for outputs*
Randomization weight strata	body weight stratum (≤ 100 kg, >100 kg)		Weight strata	a

Table 2-2 Subgroup analyses

Endpoint/analysis	Randomization weight strata	Previous psoriasis therapy*
Co-primary endpoints:		
PASI 90 response at Week 12	X	X
IGA 0/1 response at Week 12	X	X
Secondary endpoints:		
PASI 75 response at Week 12	X	X
PASI 75 response at Week 4	X	X
PASI 90 response at Week 16	X	X
PASI 100 response at Week 16	X	X
IGA 0/1 response at Week 16	X	X
PASI 100 response at Week 12	X	X
PASI 75 response at Week 16	X	X
PASI 90 response at Week 52	X	X
[redacted]		

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, Ustekinumab, 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:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity
- Smoking status at baseline
- Weight categories (≤ 100 kg, > 100 kg)

Psoriasis-specific baseline characteristics and history of disease will be summarized as well: baseline PASI, baseline PASI (≤20, >20), baseline total BSA, baseline IGA mod 2011 score (at least mild, moderate, severe), severity of psoriasis (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)), psoriatic arthritis (yes, no), time since diagnosis of psoriasis, time since diagnosis of psoriatic arthritis, previous exposure to biologic systemic psoriasis therapy, previous exposure to systemic psoriasis therapy, previous exposure to non-biologic systemic psoriasis therapy, previous failure to biologic systemic psoriasis therapy, previous failure to systemic psoriasis therapy, previous failure to non-biologic systemic psoriasis therapy (including phototherapy and photo- chemotherapy)

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.

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 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.

Summaries for family medical history will be summarized by categories and treatment group.

Smoking history will be summarized by treatment group.

Unless otherwise specified, analyses will be based on the randomized set.

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 and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

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

2.4 Treatments (study treatment, rescue medication, 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 and ustekinumab injections will be summarized by treatment group by means of contingency tables.

In case it cannot be identified from the data collected or assumed from the planned treatment whether an injection contained placebo or ustekinumab, it will be assumed that the syringe contained ustekinumab. This applies for example to the ustekinumab treatment group for subjects with baseline body weight ≤ 100 kg (in which subjects should receive both an ustekinumab and a placebo injection) if only one injection is given. If the medication pack number is not available, it will be assumed that the ustekinumab injection was applied.

If this scenario occurs for subjects in the secukinumab treatment group or in the ustekinumab treatment group with baseline body weight > 100 kg, when subjects should receive two identical injections, it will be assumed that they received secukinumab or secukinumab placebo or ustekinumab, respectively, as planned.

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”, “≥12 weeks”, “≥16 weeks”, “≥20 weeks”, “≥24 weeks”, “≥28 weeks”, “≥40 weeks” and “≥52 weeks”.

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

The analyses of duration of exposure described above will be done for the treatment period up to Week 16 for the interim analysis, with the last category "≥16 weeks".

2.4.1.1 Visit window

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-3. 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 2-3 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 2-18
Week 4	4	29	Day 19-57
Week 12	12	85	Day 58-99
Week 16	16	113	Day 100-155
Week 28	28	197	Day 156-239
Week 40	40	281	Day 240-323
Week 52	52	365	Day 324-421

* 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. weight, laboratory, [redacted]), visit windows defined in Table 2-3 will be combined. For example, if a parameter is measured at Week 12 and Week 28 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 28 will extend from Day 100 to Day 239

(combining Week 13 to Week 28). If more than one assessment falls into the interval, the rules defined in Section 2.4.1.2 below are applied.

Of note: subject's height 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 421) it is not assigned an analysis visit and will be listed under label "After Week 52".

2.4.1.2 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 2-4).

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 2-4 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 for [redacted] 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.

[redacted]

Timing of measurement	Type of data	Rule
		[redacted]
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.

2.4.2 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.

Psoriasis specific summaries of prior and/or concomitant medication will be presented as in Table 2-5, but as well for topical, phototherapy and photochemotherapy (yes/no) using the randomized set.

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.

Drug contraindication will be summarized by drug type and treatment group.

Table 2-5 Subgroups based on the previous psoriasis therapy

Level 1 description	Level 1 outcome	Level 2 description	Level 2 outcome
previous therapy	yes/no		
systemic	no		
	yes	number	1
			2
			>=3
		failure*	no
			yes
biologic	no		
	yes	failure*	no
			yes
		type of previous biologic	
		anti-p40	no
			yes
		anti-TNF	no
			yes
non-biologic systemic	no		
	yes	failure*	no
			yes
		failure* to at least 2	no
			yes

only selected subgroups will be used for reporting

*: at least one therapy with lack of primary efficacy or lack of secondary efficacy or lack of tolerability

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The co-primary endpoints are PASI 90 response and IGA 0 or 1 response at Week 12. The analysis of the primary 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 2-6.

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 2-6).

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

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

Table 2-6 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)

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 2-7) 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 2-7 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.

2.5.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-8.

Table 2-8 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 90 response at Week 12	X	X			X*
IGA 0/1 response at Week 12	X	X			X*
PASI 75 response at Week 12	X	X			X*
PASI 75 response at Week 4	X	X			
PASI 90 response at Week 16	X	X			X*
PASI 100 response at Week 16	X	X			X*
IGA 0/1 response at Week 16	X	X			X*
PASI 100 response at Week 12	X	X			X*

Variable(s)	Summary statistics for binary/ categorical data	Logistic regression	Summary statistics for continuous data	Time-to-event analysis	Graphs
PASI 75 response at Week 16	X	X			X*
PASI 90 response at Week 52	X	X			
[redacted]					
* dot plot; [redacted]					

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis for PASI 90 response and IGA 0 or 1 response at Week 12 is that secukinumab is not superior to ustekinumab in the proportion of subjects with PASI 90 response and IGA 0 or 1 response at Week 12.

Let p_j denote the proportion of PASI 90 responders at Week 12 for treatment group *j* and r_j denote the proportion of IGA 0 or 1 responders at Week 12 for treatment group *j*;

j=0, 1, where

- 0 corresponds to ustekinumab,
- 1 corresponds to secukinumab.

The following hypotheses will be tested:

$H: H_1 \cup H_2$ versus $H_A: H_{A1} \cap H_{A2}$

$H_1: p_1 - p_0 \leq 0$ versus $H_{A1}: p_1 - p_0 > 0$,

$H_2: r_1 - r_0 \leq 0$ versus $H_{A2}: r_1 - r_0 > 0$,

In other words:

H: secukinumab is not superior to ustekinumab with respect to either PASI 90 response at Week 12 or IGA 0 or 1 response at Week 12 or both

H_1: secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 12

H_2: secukinumab is not superior to ustekinumab with respect to IGA 0 or 1 response at Week 12

The primary analysis method for PASI 90 and IGA 0 or 1 response at Week 12 will be evaluated using logistic regression model with treatment group, body weight stratum (≤100 kg, >100 kg) and baseline PASI score as explanatory variables (see Section 5 Appendix). Odds ratios will be

computed for comparisons of secukinumab versus ustekinumab utilizing the logistic regression model fitted. In case of non-convergence, risk difference (95% confidence interval) between secukinumab and ustekinumb and p-value get from t-test will be provided.

The hypotheses H_1 and H_2 will both be tested at α level = 2.5% (one-sided) and significant results will only be achieved if both hypotheses are rejected (i.e., if only one hypothesis is rejected and the other hypothesis is not rejected, superiority of secukinumab cannot be demonstrated).

The primary analysis set will be the FAS.

Summary statistics and figures will be provided as described in Section 5.4.6. Details in sensitivity analysis are provided in Section 2.5.4.

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.

Modified non-responder (mNRI) imputation and pure non-responder (pNRI) 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 for modified non-responder imputation method 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 only if visit x-1 or visit x+1 are scheduled 4 weeks or less from visit x. Otherwise missing data at visit x will be imputed with non-response, except for the missing data at last visit in the treatment period.

Summary tables for PASI scores and IGA mod 2011 categories will be imputed using MI and LOCF method.

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

2.5.4 Supportive analyses

Sensitivity analyses will be performed as follows:

(A) 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 pure non-responder (pNRI) imputation and modified non-responder (mNRI) imputations instead of multiple imputation for missing values.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary endpoints of this study are planned as follow:

- speed of onset (PASI 75 at Week 4)
- PASI 75, PASI 90, PASI 100 and IGA 0/1 response at Week 16
- PASI 75 and PASI 100 at Week 12
- PASI 90 at Week 52

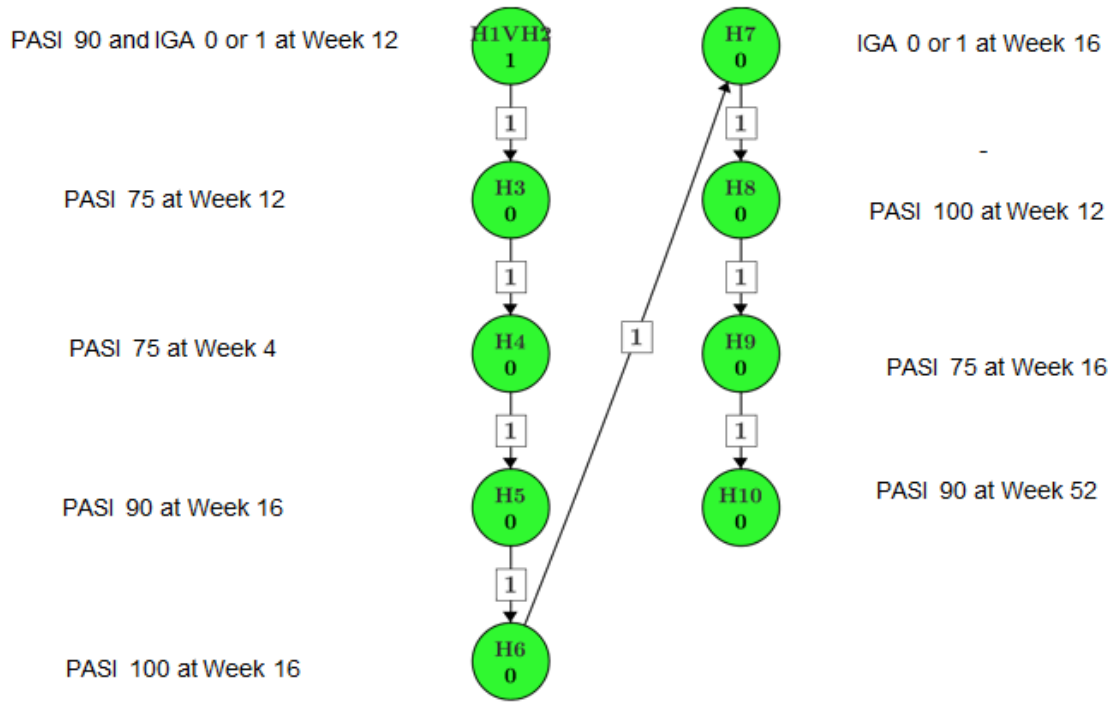
The null hypotheses for secondary objectives are as follows:

- H_3: secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 12
- H_4: secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 4
- H_5: secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 16
- H_6: secukinumab is not superior to ustekinumab with respect to PASI 100 response at Week 16
- H_7: secukinumab is not superior to ustekinumab with respect to IGA 0 or 1 response at Week 16
- H_8: secukinumab is not superior to ustekinumab with respect to PASI 100 response at Week 12
- H_9: secukinumab is not superior to ustekinumab with respect to PASI 75 response at Week 16
- H_{10}: secukinumab is not superior to ustekinumab with respect to PASI 90 response at Week 52

2.6.2 Statistical hypothesis, model, and method of analysis

The following hypotheses will be tested sequentially and are included in the hierarchical testing strategy and type-I-error will be set such that a family-wise type-I-error of $\alpha = 2.5\%$ (one-sided) is kept. 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



The secondary efficacy variables involved in the above testing strategy will be analyzed analogously to the primary endpoints. i.e., logistic regression model with treatment group, body weight stratum (≤100 kg, >100 kg) and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab versus ustekinumab utilizing the logistic regression model fitted.

The testing sequence will continue to H_3 at α (one-sided) only if both H_1 and H_2 have been rejected at α (one-sided). Similarly, the testing sequence will continue to H_4 at α (one-sided) only if H_3 testing has been rejected. In case, H_9 has been rejected at α (one-sided), the corresponding alpha (α) will be passed to the next hypotheses corresponding H_{10}.

2.6.3 Handling of missing values/censoring/discontinuations

See Section 2.5.3.

2.7 Analysis of secondary efficacy objective(s)

No other secondary efficacy objectives were analyzed.

2.7.1 Secondary endpoints

Not applicable.

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 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 treatment period up to Week 16 for the Week 16 interim analysis and all data for the final analysis. The following groups will be used:

- AIN457 300 mg: all subjects who are randomized to secukinumab group
- Ustekinumab: all subjects who are randomized to ustekinumab group

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

2.8.1 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 16)	• 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 Ustekinumab 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 presented for the treatment period up to Week 16 for W16 interim analysis, and treatment period including all data for final analysis. 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 reported separately by standardized or customized MEdDRA queries (SMQ or CMQ/NMQ). 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.

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.

2.8.1.1 Adverse events of special interest / grouping of AEs

Crude incidence rate and 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 [STANDARD](NMQ) (narrow)	Include Crohns (PT) and Ulcerative colitis (PT) and others
Opportunistic infections [FINGOLIMOD](CMQ)	
Candida infections (HLT)	
Herpes viral infections (HLT)	Both Oral and other are included
Staphylococcal infections (HLT)	
MACE (MI, Stroke, Cardiovascular death) [AIN457](NMQ)	
Malignant or unspecified tumours (SMQ)	Including BCC, SCC in SMQ
Malignant or unspecified tumours (SMQ excl BCC and SCC) [AIN457](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 CREDI at the path [redacted]

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.

2.8.2 Deaths

Separate summary and listing will be provided for deaths.

2.8.3 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
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
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	1) 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. 2) 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 notably abnormal laboratory values (reference to Protocol Amendment 1, Appendix 1) and newly occurring or worsening abnormal laboratory data by CTC grades. 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. No analysis will be done for these measurements.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

A standard 12-lead ECG will be performed at screening to assess the eligibility of subjects. No analysis will be done for ECG measurements.

2.8.4.2 Vital signs

There will be two measurement of vital sign at each visit. The averaged value will be used for 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:

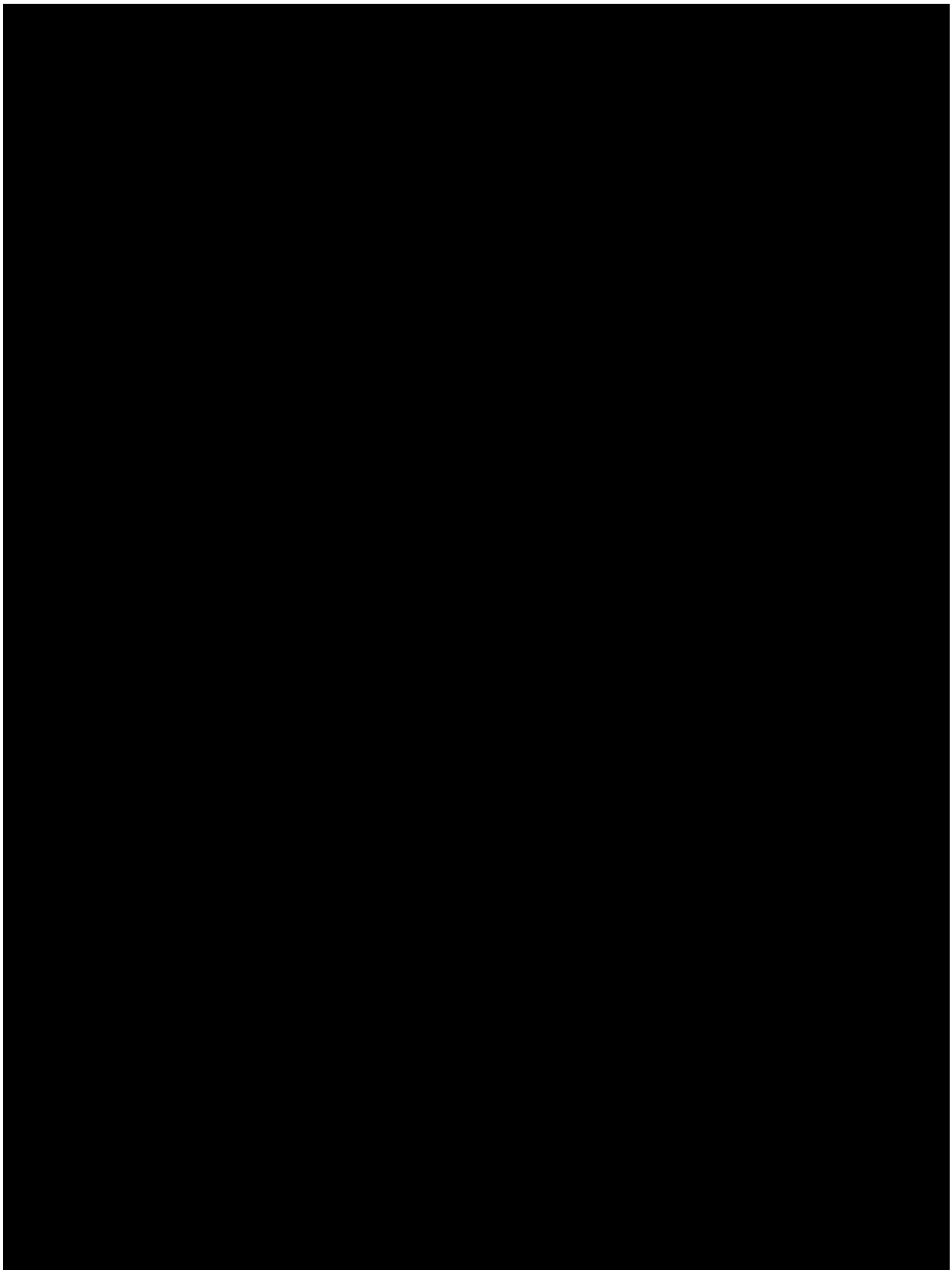
change from baseline = post-baseline value – baseline value

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]

2.14 Interim analysis

Week 16 interim analysis will be performed after all subjects have completed Week 16 visit.

Additional analyses may be performed to support health authority interactions as necessary.

At the End of Study, a final analysis of all data collected up to last study visit (Week 52 or F8 as applicable) will be performed when all subjects have completed the last study visit.

3 Sample size calculation

The total sample size is 1100 subjects, i.e. using a balanced randomization 550 subjects will be randomized to each treatment group.

The secukinumab dose regimen versus ustekinumab with respect to the co-primary endpoints PASI 90 and IGA 0/1 at Week 12 are tested at α=2.5% (one-sided). The response rates are computed based on CLEAR (CAIN457A2317) study data. The assumed response rates and power are shown in. The power calculations are based on chi-square test (nQuery Advisor 7.0, two group chi-square test of equal proportions).

Table 3-1 Power to show superiority of secukinumab versus ustekinumab for co-primary endpoints

Endpoints	Secukinumab 300 mg Response (%)	Ustekinumab Response (%)	Power
PASI 90 at Week 12	66%	52%	>99%
IGA 0/1 at Week 12	77%	64%	>99%

Note: one-sided type-I-error=2.5%, N=550 per group

If the assumed PASI 90 response rate at week 12 for secukinumab is 66% and for ustekinumab is 52%, the power to reject the corresponding null hypothesis is greater than 99%. Similarly, if the assumed IGA 0/1 response rate at week 12 for secukinumab is 77% and for ustekinumab is 64%, the power to reject the corresponding null hypothesis is also greater than 99%. Details for other key secondary endpoints are provided in Table 3-2.

The secukinumab dose regimen versus ustekinumab with respect to the secondary endpoints are tested at α=2.5% (one-sided). The response rates are computed based on unpublished CLEAR (CAIN457A2317) study data.

Table 3-2 Power to show superiority of secukinumab versus ustekinumab for secondary endpoints

Endpoints	Secukinumab 300 mg Response (%)	Ustekinumab Response (%)	Power
PASI 75 at Week 12	88%	79%	97%
PASI 75 at Week 4	47%	21%	>99%
PASI 90 at Week 16	74%	55%	>99%
PASI 100 at Week 16	40%	24%	>99%
IGA 0/1 at Week 16	80%	65%	>99%
PASI 100 at Week 12	34%	23.5%	96%
PASI 75 at Week 16	90%	82%	96%
PASI 90 at Week 52	70%	60.5%	90%

Note: one-sided type-I-error=2.5%, N=550 per group

4 Change to protocol specified analyses

A pure non-responder (pNRI) imputation for the primary endpoints will be provided as supportive analyses.

5 Appendix

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 as one-sided for hypothsis testings and as two-sided for other analysis. Two-sided 95% confidence intervals will be displayed.

Hypothesis testings will be based on one-sided p-values that treatment effect is in favor of Secukinumab. The level of significance will be set to 2.5% (one-sided, family-wise type-I-error).

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 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.

[redacted]

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, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote.

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

5.3 Laboratory parameters derivations

See Section 2.8.3.

5.4 Statistical models

5.4.1 Analysis of continuous data

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, [redacted] summary statistics will be derived for absolute and percentage changes from baseline.

5.4.2 Analysis of binary (and categorical) data

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 $p > 0, (L = 0 \text{ for } p = 0)$,

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

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 ustekinumab 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.

5.4.3 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 stratum and baseline PASI score. Odds ratios will be computed for comparisons of secukinumab versus ustekinumab utilizing the logistic regression model fitted.

If response rates are 0% or 100% in one of the treatment groups odds ratio estimate and p-values 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.

Logistic regression will be applied to response variables at each visit.

If logistic regression model does not converge 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 weight stratum, followed by baseline PASI;
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 stratum (≤100 kg, >100 kg) and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab versus ustekinumab 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, the weight stratum variable will not be fitted in the logistic regression model.

5.4.4 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, 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 4572326 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> <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 5.4.6.2. This analysis will be done by _IMPUTATION_ for the comparison to the ustekinumab 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. Ustekinumab” <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 estimate;
  Stderr stderr;
RUN;
ODS LISTING;

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

5.4.5 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 90, 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.
- for treatment comparisons the hazard ratio derived via Cox regression as well as log-rank test and Wilcoxon test.

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

Treatment period: ">12 weeks to <=16 weeks", ">16 weeks to <=28 weeks", ">28 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 90	All PASI 90 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 90 observed	End of treatment period as per CRF disposition page	Censor (if Anti-psoriasis ConMed taken before the event)	Study phase discontinu-ation with reason "lack of efficacy"
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 Anti-psoriasis ConMed taken before the event)	Study phase discontinu-ation with reason "lack of efficacy"

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

5.4.6 Crude incidence and related risk estimates

5.4.6.1 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.

5.4.6.2 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 5.4.6.3. If the relative risk is not well approximated by the odds ratio but asymptotic normality is questionable, STATXACT will be used.

5.4.6.3 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. ustekinumab) 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.

5.4.6.4 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.

5.4.7 Exposure adjusted incidence rate and related risk estimates

5.4.7.1 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.

5.4.7.2 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

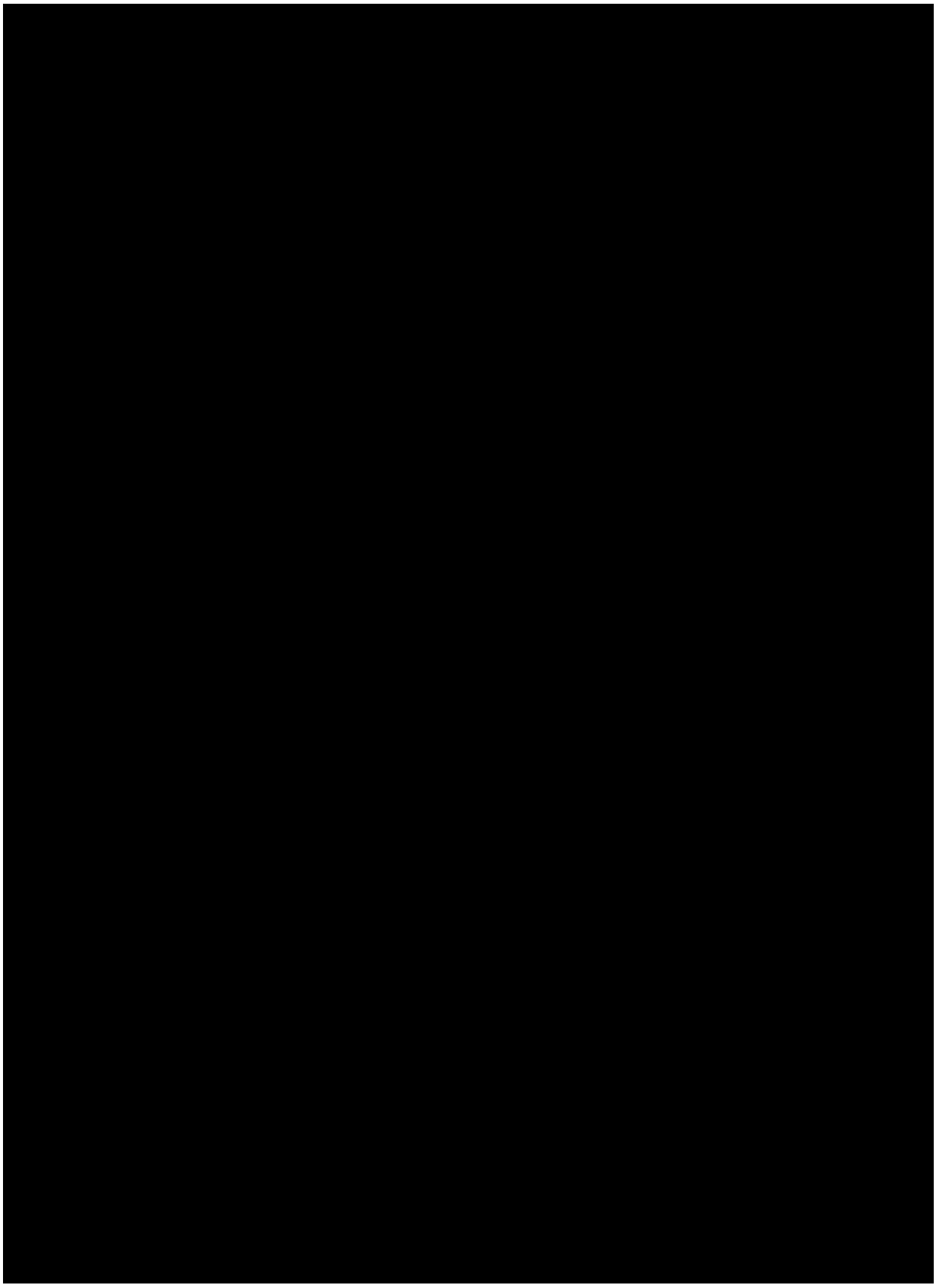
Protocol deviations for exclusion from analysis sets are defined in Table 5-2.

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: INCL02a; OTH15	Misrandomized subject
Safety	DVSPID: INCL02a; OTH15	Subjects who did not take any study treatment

INCL02a: ICF missing or not signed

OTH15: Severe ICH-GCP non-compliance of study site



[redacted]

6 Reference

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