NOVARTIS

Clinical Development - General Medicine

Secukinumab/AIN457

Clinical Trial Protocol CAIN457A2310 / NCT02471144

A randomized, double-blind, placebo- and active controlled multicenter trial to demonstrate efficacy of subcutaneous secukinumab compared to placebo and etanercept (in a single-blinded arm) after twelve weeks of treatment, and to assess the safety, tolerability, and long-term efficacy in subjects from 6 to less than 18 years of age with severe chronic plaque psoriasis

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Outcome for update	Section and title impacted (Current)
13Apr2017	First		NA
03-Jan-2019	Prior to week 24 DB lock	Update for W24 Primary endpoint analysis	Section 1.1 Study design Section 1.2 Study objectives and endpoints Section 2.1 Data analysis general information Section 2.1.1.3 Screening, baseline and post-baseline definitions Section 2.3 Subgroups of interest Section 2.4.1 Patient disposition Section 2.4.2 Demographics and other baseline characteristics
16-Jan-2019	Prior to week 24 DB lock	Updated MI and logistic regression related details	Section 5.1.2.2 Exact Logistic regression Section 5.1.2.3 Multiple imputations for response variables
05-Feb-2019	Prior to week 24 DB lock	Updated Liver event related section and Time to event related section.	Section 5.1.5 Analysis of time-to-event data Section 5.2.4 First diagnosis date (PsO, PsA) imputation
27-Mar-2019	Prior to week 24 DB lock	Updated "Section 2.9.4.2" for vital sign criteria and "section 1.2" for primary endpoint analysis related details. Updated Update for W24 Primary endpoint analysis related information	Section 2.9.4 Other safety data Section 1.2 Study objectives and endpoints Section 2.2 Analysis sets Section 2.4.2 Demographics and other baseline characteristics Section 2.4.3 Medical history Section 2.9.4.2 Vital signs Section 2.15.1 Children's Quality of Life Index (CDLQI) Section 2.15.5 Interim analysis

Date	Time point	Outcome for update	Section and title impacted (Current)
29-Mar-2019	Prior to week 24 DB lock	Added note that only "<18 years of age subjects will include in CDLQI summary report.	Section 5.1.5 Analysis of time-to-event data
07-APR-2019	Prior to week 24 DB lock	Updated demographic and liver event related information.	Section 2.4.2Demographics and other baseline characteristics Section 2.9.3.1 Liver events
24-Apr-2019	Prior to week 24 DB lock	Updated exact logistic regression model information., visit window information	Section 5.1.2.2 Exact Logistic regression Section 2.1 Data analysis general information Section 2.1.1.5 Visit windows Section 2.6.4 Handling of missing values/censoring/discontinuations Section 2.9.1.1 Adverse events of special interest / grouping of AEs
30-APR-2019	Prior to week 24 DB lock	Updated table 1-1 information for W24PEA, updated data analysis general section, updated table 2-1, added table 2-2b,	Section 1 Induction Section 1.2 Study objectives and endpoints Section 2.1.1.1 Study treatment Section 2.6.3 Statistical hypothesis, model, and method of analysis Section 2.9.1 Adverse events (AEs)
01-MAY-2019	Prior to week 24 DB lock	[redacted] [redacted] 2.14 Growth and Physical development 2.15.5 Interim analysis 4 Change to protocol specified analyses 5.1.2.2 Exact Logistic regression -exact logistic regression model related details. Table 5.1 Time to event: definition of risk set,	[redacted] Section 2.14 Growth and Physical development Section 2.15.5 Interim analysis Section 4 Change to protocol specified analyses Section 5.1.2.2 Exact Logistic regression -exact logistic regression model related details. Section 5.1.5 Analysis of time-to-event data Section 2.9.3 Laboratory data

Date	Time point	Outcome for update	Section and title impacted (Current)
		timing and censoring by variable - updated ConMed censoring details. Table 2-13 CTCAE grades for laboratory parameters to be analyzed, for eGFR related update	
04-MAY-2019	Prior to week 24 DB lock	Updated the reference section	Section 6 Reference
02-Aug2019	After DB lock	MI section remove "baseline IGA score and failure to at least one previous biologic (yes/no)" from the PROC MI section.	Section 5.1.2.3
06-Aug-2019	After DB lock	[redacted] Updated CDLQI scoring related details. Added extended Week 12 visit window details Updated AE and dose exposure section for IRT dosing error subject group Updated additional analysis related details for PASI IGA and CDLQI related analysis. Updated multiple imputation, exact logistic regression and risk difference related code section.	Section 2.10 Section 5.6.1 Section 2.1.1.5 Section 2.9.1 Section 2.7.3 Section 5.1.2.2, Section 5.1.2.3
15-Aug-2019	After DB lock	Added a section for data-driven analysis	Section 4.1
17-Oct-2019	After Week 24 PEA DBL, but before Week	Added text to clarify the up to week 52 maintenance period	Section 2.1.1.1 Study treatment

Date	Time point	Outcome for update	Section and title impacted (Current)
	52 IA DBL		
		Added text to clarify for the efficacy treatment group used for entire treatment period and some text included in Visit windows section	Section 2.1.1.1 Study treatment
		Added 'entire treatment period' in the description of the actual treatment derivations.	Section 2.2 Analysis sets
		Added duration of exposure to study treatment will also be summarized by age strata.	Section 2.5.1 Study treatment / compliance
		Added Maintenance period (up to week 52) in table 2-11	Section 2.9.1 Adverse events (AEs)
		Added exposure adjusted incidence rates for the entire treatment period, by subgroups.	Section 2.9.1 Adverse events (AEs)
		Added subheadings for clarification.	
		Removed cholesterol and triglycerides, since per protocol cholesterol and triglycerides are not analyzed. Also, clarified chemistry glucose was only tested based on glucose urine dipstick result, so only needs to be listed and not tabulated.	Section 2.9.3 Laboratory data
		Clarified ranges for Grade 2 and Grade 3 for eGFR in table 2-13	
		Added analysis of hematology CTCAE grades presented by age strata and by body weight strata.	
		[redacted]	[redacted]

Date	Time point	Outcome for update	Section and title impacted (Current)
		[redacted]	[redacted]
		Added figure of change from baseline in CDLQI total score over time.	Section 2.15.1 Children's Quality of Life Index (CDLQI)
		Added Week 52 interim analysis cut-off date information.	Section 2.15.5 Interim analysis
		Added 'Analyses by age strata excluding IRT dose affected subjects' and 'Analyses treating the IRT dose error affected results as missing'.	Section 4.1 Additional and data driven analysis
		Clarified LOCF does not need to be applied to the individual question scores (since only subscales and total are analyzed).	Section 5.6.1 CDLQI scoring
		Text added for version control	Section 1 Introduction
30-Jan-2020		Updated Multiple imputation derivation related details.	Section 5.1.2.3 Multiple imputations for response variables
[redacted]	[redacted]	[redacted]	[redacted]

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List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
CDLQI	Children's Dermatology Life Quality Index
CHAQ	Childhood Health Assessment Questionnaire
CHMP	Committee for Medicinal Products for Human Use
COVID	Coronavirus Disease
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CTCAE	Common Terminology for Adverse Events
[redacted]	[redacted]
DMC	Data Monitoring Board
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GGT	Gamma-glutamyl transferase
HA	Health Authorities
[redacted]	[redacted]
IGA mod 2011	Novartis Investigator's Global Assessment modified in 2011
IRT	Interactive Response Technology
LOCF	Last Observation Carried Forward
MACE	Major Adverse Cardiovascular Events
MAP	Master Analysis Plan
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities

MI	Multiple Imputation
MMRM	Mixed- effects Repeated Measures Model
[redacted]	[redacted]
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PEA	Primary Endpoint Analysis
PD	Protocol Deviation
[redacted]	[redacted]
[redacted]	
PT	Preferred Term
QTcF	Fridericia QT Correction
SAE	Serious Adverse Event
s.c.	Subcutaneous
SD	Standard Deviation
SOC	System Organ Class
[redacted]	[redacted]
TBL	Total Bilirubin
VAS	Visual Analogue Scale
WBC	White blood cells

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1 Introduction

Data will be analyzed by [redacted] according to the data analysis section 9 of the 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 contains the detailed statistical and analytical plans for full analysis of CAIN457A2310 study and covers aspects for Week 24 primary endpoint analysis (PEA) and Week 52 full analysis, with reference to the study protocol amendment 3.

SAPs were finalized and approved with version controls:

- A2310 SAP 1.0 (dated 14-April-2017): first version of the analysis plan
- A2310 SAP amendment 1.0 (dated 06-May-2019): amendment to the SAP after dry run prior to the Week 24 database lock
- A2310 SAP addendum (dated 07-Sep-2019): addendum to the SAP post Week 24 database lock
- A2310 SAP amendment 2.0 (dated 23-Oct-2019): amendment to the SAP after dry run prior to the Week 52 database lock (current version)
- A2310 SAP amendment 3.0 (dated 18-Dec-2020): amendment to the SAP prior to the Week 104 database lock (current version)

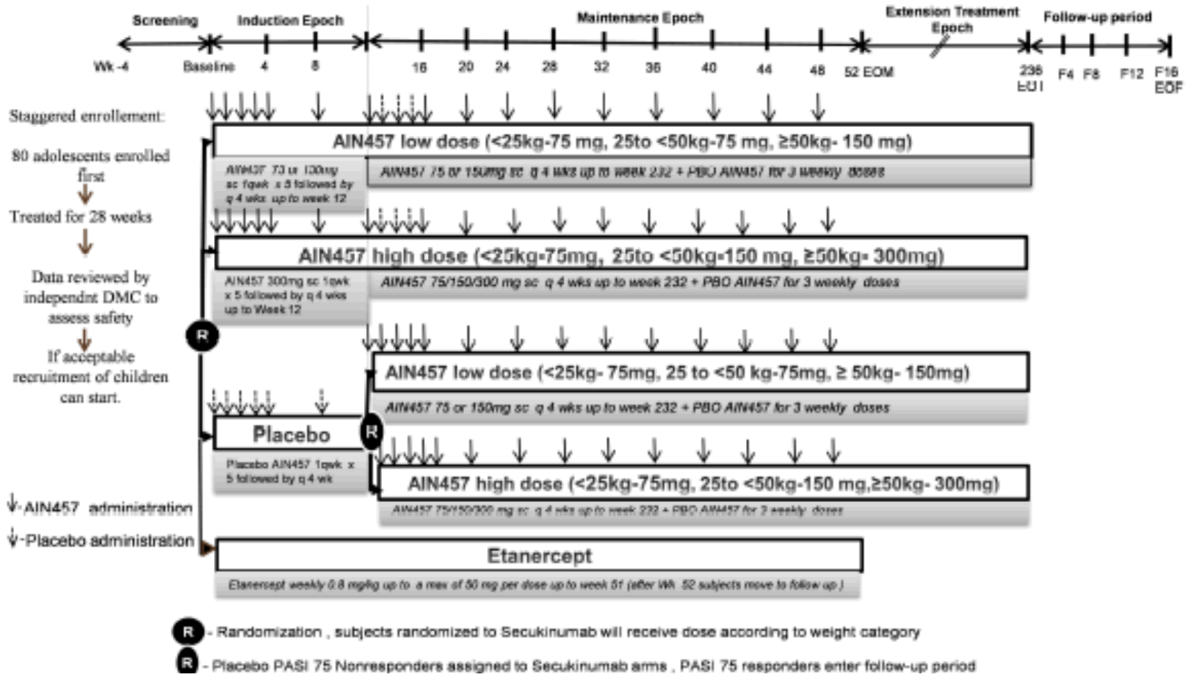
1.1 Study design

This is a multicenter, randomized, double-blind, placebo-and active-controlled (etanercept in single blinded arm) study in pediatric subjects aged 6 years to less than 18 years with severe chronic plaque psoriasis. Approximately 160 subjects aged 6 years to <18 years will be enrolled, of which at least 30 pediatric subjects will be 6 years to <12 years old. In reality around 40-45 patients will be needed to meet the requirement of recruiting about 30% of subjects in the < 25kg weight group.

Subjects will be randomized using a 1:1:1:1 ratio into one of the treatment arms: secukinumab low dose, secukinumab high dose, etanercept or placebo. The randomization will be stratified by age (<12 years or ≥12 years) and weight (<25 kg, 25-<50 kg, ≥50kg) at randomization. Subjects randomized to the placebo group will be pre-assigned to either the low- or high-dose group of secukinumab, at the Randomization visit, in case they are not achieving a PASI 75 response as assessed at Week 12.

The study consists of 5 Epochs: screening (up to 4 weeks), induction (of 12 weeks), maintenance (of 40 weeks), extension treatment epoch (open-label of 184 weeks) and post-treatment follow-up epoch (of 16 weeks). The detailed information of the study design is described in Figure 1-1.

Figure 1-1 Study design



The following study periods will be considered for analysis:

- **Screening period** (before Randomization)
- **Induction period** (Randomization to Week 12 pre-dose), including follow-up period (F4, F8, F12 and F16 (EOF) visits) for prematurely discontinued subjects before Week 12 completion. For placebo PASI 75 responders at Week 12, subjects will enter follow-up period after Week 12, including the first visit F4 and four weeks later visit EOF at F8.
- **Maintenance period** (Week 12 dose to Week 52 pre-dose), including follow-up period (F4, F8, F12 and F16 visits) for prematurely discontinued subjects before Week 52 completion, and for etanercept patients with the completion of the maintenance epoch.
- **Extension period** (Week 52 dose until Week 236 (EOT)), including follow-up period (F4, F8, F12 and F16 visits) for prematurely discontinued subjects before Week 236 completion.
- **Entire treatment period** (Randomization to Week 236 (EOT)), for safety analysis, exposure including follow-up period up to last dose + 84 days.
- **Entire study period** (Randomization to end of study (EOS)), including follow-up period (F4, F8, F12 and F16 visits).

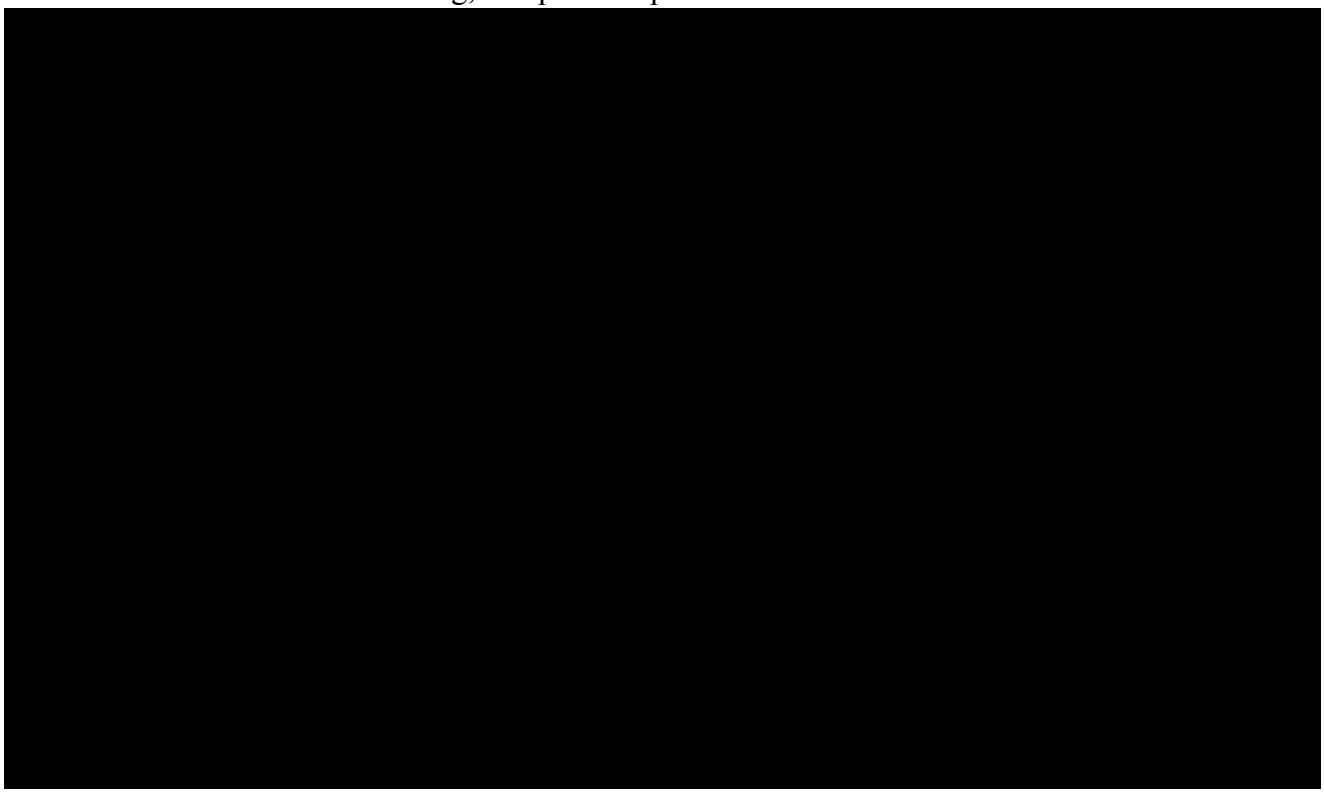
1.2 Study objectives and endpoints

The primary objective of the study is to demonstrate the superiority of secukinumab (low and high dose) in pediatric subjects with severe chronic plaque psoriasis with respect to both PASI

75 and IGA mod 2011 0 or 1 response (co-primary endpoints) at Week 12, compared to placebo.

Following are the secondary objectives:

- To demonstrate superiority of secukinumab (low and high dose) in subjects with severe chronic plaque psoriasis with respect to PASI 90 response at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaques psoriasis with respect to PASI 50 and PASI 100 at Week 12, compared to placebo.
- To assess efficacy of secukinumab in subjects with severe chronic plaque psoriasis with respect to PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 at Week 16 and over time up to Week 52 (will consider up to week 24, for Week 24 PEA).
- To assess the efficacy of secukinumab with respect to changes in PASI score and IGA mod 2011 score at Week 12, compared to placebo, and over time up to Week 52 (will consider up to week 24, for Week 24 PEA).
- To investigate the effects of treatment with secukinumab with respect to changes in CDLQI at Week 12, compared to placebo, and over time up to Week 52 (will consider up to week 24, for Week 24 PEA).
- To investigate the effects of treatment of secukinumab with respect to CDLQI 0 or 1 achievement at Week 12, compared to placebo, and over time up to Week 52 (will consider up to week 24, for Week 24 PEA).
- To evaluate the effects of treatment of secukinumab on disability at Week 12 and over time up to Week 52 (will consider up to week 24, for Week 24 PEA) by use of CHAQ©, for subjects with history of psoriatic arthritis.
- To investigate the clinical safety and tolerability of secukinumab as assessed by growth, weight gain, tolerability of s.c. injections, vital signs, clinical laboratory variables, ECGs, and adverse events monitoring, compared to placebo.



[redacted]

Table 1-1 Primary, secondary [redacted] efficacy variables

Variable	Type
PASI 75 at Week 12, compared to Placebo	Co-primary
IGA mod 2011 0 or 1 response at Week 12, compared to Placebo	Co-primary
PASI 90 response at Week 12, compared to Placebo	Key secondary
PASI 50, PASI 75, PASI 90, PASI 100, IGA mod 2011 0 or 1 compared to Placebo over time up to Week 52 (or Week 24, for PEA)	Secondary
Change from baseline in PASI score over time up to Week 52 (or Week 24, for PEA)	Secondary
IGA mod 2011 score over time up to Week 52 (or Week 24, for PEA)	Secondary
Change in CDLQI over time up to Week 52 (or Week 24, for PEA)	Secondary
CDLQI 0 or 1 achievement over time up to Week 52 (or Week 24, for PEA)	Secondary
Change in CHAQ over time up to Week 52 (or Week 24, for PEA)	Secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

This document covers the statistical analysis plan for Week 24 PEA analysis, Week 52 analysis and final analysis.

[redacted] will perform the analyses at week 24 and week 52 and final analysis. Statistical software SAS version 9.4 or later will be used.

Summary statistics for continuous variables will be presented with n, mean, standard deviation, minimum, lower quartile (Q1), median, upper quartile (Q3) and maximum for observed values and change from baseline. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

P-values will be presented as one-sided for hypothesis testing and as two-sided for other analysis. Two-sided 95% confidence intervals will be displayed. If not otherwise specified, hypothesis testing 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). The 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.

[redacted]

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings can be presented on a separate page and do not have to be repeated as footnotes on each listing
- sort 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 than 1 favors active treatment”)
- information that can be retrieved from the statistical section of the 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. body mass index (BMI) will not be explained in 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 prefilled syringes, available as a 150 mg in 1.0 mL and as a 75 mg in 0.5 mL syringes.
- Reference treatment
  - Secukinumab placebo, secukinumab placebo available as 1 mL and 0.5 mL prefilled syringes
  - Etanercept active comparator

The treatment groups for analyses are shown in Table 2-1 and will consider as appropriate. Treatment period up to week 24/52 contains both Induction and Maintenance period.

Table 2-1 Treatment groups for analyses

Treatment group	Efficacy			Safety		
	Induction (up to week 12)	Maintenance (week 12-52)	Extension period (week 52-236)	Induction (up to week 12)	Treatment period up to week 24/52	Entire treatment / study period
Low dose Secukinumab (i.e. AIN457 Low dose)	X	X	X	X	X	
High dose Secukinumab (i.e. AIN457 High dose)	X	X	X	X	X	
Placebo	X			X		
Placebo to Low dose Secukinumab (i.e. Placebo to AIN457 Low dose)		X	X		X[a]	
Placebo to High dose Secukinumab (i.e. Placebo to AIN457 High dose)		X	X		X[a]	
Etanercept (max 50mg per dose)	X	X		X	X	X[c]
Any Low dose Secukinumab (i.e. Any AIN457 Low dose)			X		X[b]	X
Any High dose			X		X[b]	X

Secukinumab (i.e. Any AIN457 High dose)						
Any Secukinumab dose (i.e. Any AIN457 dose)				X	X	X

[a] Applicable for safety by-visit analysis

[b] Not applicable for safety by-visit analysis

[c] For subsequent analyses beyond the week 52 analysis, Etanercept will only be presented in exposure adjusted incidence rate (EAIR).

For entire treatment period efficacy analysis after week 52; Any AIN457 low dose (without remapping) and Any AIN457 High dose (without remapping) treatment groups will be consider.

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 labelled 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 labelled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose.

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained on or before the randomization (day). All assessments obtained after randomization (day) 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 (day) of study drug 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 Quality of Life assessments, Lab and ECG, if no pre-treatment value exists, values recorded after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered. And "re-randomization" for placebo group at Week 12 will not be used for baseline definition and only one baseline value will be defined referring to the first randomization.

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. 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 event is defined as assessments within last dose plus 84 days, for safety analysis (i.e., Lab, vitals and ECG).

2.1.1.5 Visit windows

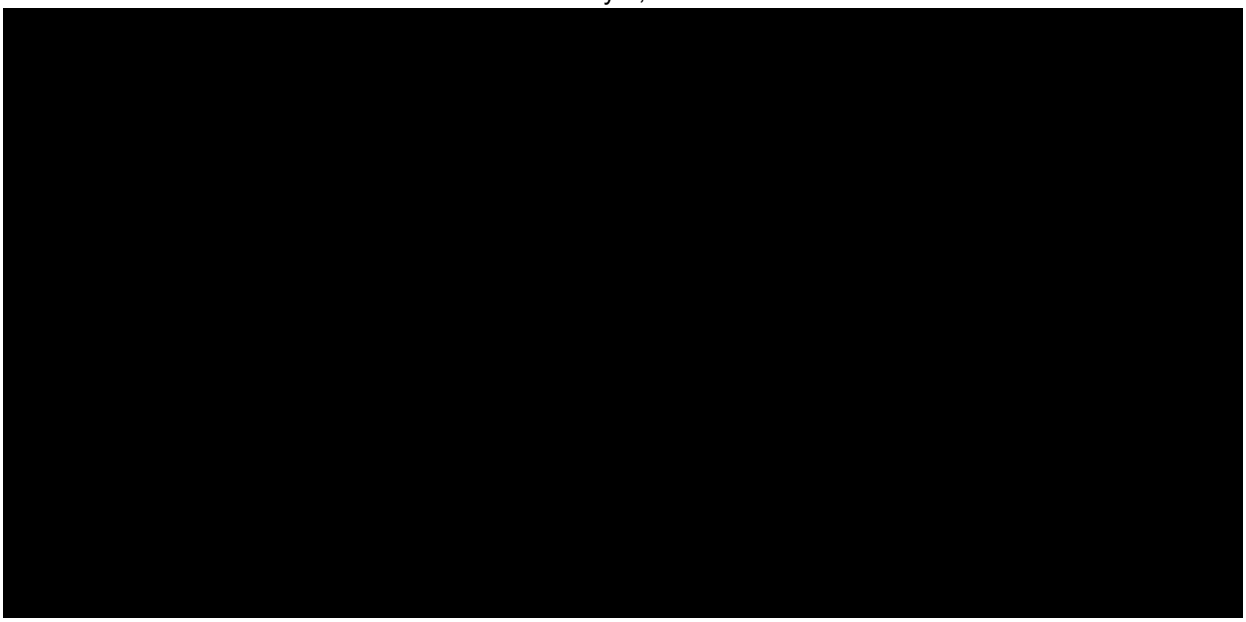
Visit-windows will be used for the data that is summarized by visit; these are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-2a [redacted], which apply to measurements taken at every visit. For assessments collected less often, different visit windows will be applied as detailed below. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Week 4 visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, then it will be re-aligned to visit window Week 8. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below. Of note, subjects are allowed to have gaps in visits.

Table 2-2a Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-to Day 1 (-28 days to Day 1 for psoriasis)
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 (EOI)	12	85	Day 72-88
Week 13	13	92	Day 89-95
Week 14	14	99	Day 96-102
Week 15	15	106	Day 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 (EOM)	52	365	Day 352-407
Week 64	64	449	Day 408-491
Week 76	76	533	Day 492-575
Week 88	88	617	Day 576-673
Week 104	104	729	Day 674-771
Week 116	116	813	Day 772-855
Week 128	128	897	Day 856-939
Week 140	140	981	Day 940-1037
Week 156	156	1093	Day 1038-1135
Week 168	168	1177	Day 1136-1219
Week 180	180	1261	Day 1220-1303
Week 192	192	1345	Day 1304-1401
Week 208	208	1457	Day 1402-1499
Week 220	220	1541	Day 1500-1583
Week 232	232	1625	Day 1584-1639
Week 236 (EOT)	236	1653	Day 1640-1667
Week 240 (F4)	240	1681	Day 1668-1695
Week 244 (F8)	244	1709	Day 1696-1723
Week 248 (F12)	248	1737	Day 1724-1751
Week 252 (F16 EOF)	252	1765	Day 1752-1779

EOI: End of Induction Period; EOM: End of Maintenance Period; EOT: End of Treatment; EOF: End of Follow-up



For parameters, which are not collected at every visit (e.g. weight), visit windows defined in the tables above will be combined. E.g., if a parameter is measured at Week 12 and Week 24 only, then 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, then the rules defined in Section 2.1.1.6 are applied.

Maintenance period visits will not be mapped into induction period, and induction period visits will not be mapped into maintenance period. For example, if a subject is coming late for the Week 12 visit (induction period), and the visit would be fall into the Week 13 (maintenance period) visit window, then it would not be mapped to maintenance period for the analysis but will still be considered as part of induction period. Of note, for subjects who discontinue in induction/maintenance period, i.e. not moving into maintenance/extension period, measurements taken in follow-up period would still be considered for induction/maintenance period.

In addition, sensitivity analyses for PASI and IGA mod 2011 0/1 response parameters will be performed based on extended Week 12 visit window from Day 72 to Day 102. See Section 4.1 for details.

2.1.1.6 Multiple assessment 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 2-3).

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 will be chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record will be selected. It is noted that in the analyses performed, *worst* case will be always well defined (e.g., for urine protein values "+" and "++", the worst case will be defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-3 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3
Post-baseline efficacy	All data except CDLQI, CHAQ	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), then the earlier one will be used. If two measurements are taken on the same day, then the first one using eCRF visit number. If two measurements have been taken on the same day and same visit, then the worst measurement will be used.
Post-baseline efficacy	CDLQI, CHAQ	The measurement closest to the target day will be used. In the event two measurements are taken equally apart then the earlier one will be used. If two measurements are taken on the same day, the worst measurement will be used. If two measurements have the same value, select then the first one using eCRF visit number.
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g. 1 day before target date and 1 day after), the first one will be used. If two measurements are taken on the same day, then the first one will be used (using the time). If two measurements are taken on the same date/time, then the first visit number will be used (assuming this is the planned visit). If two measurements are taken on the same date/time/eCRF visit number, then the average value of these two results will be used.

Post-baseline safety	Notable abnormalities (e.g. vital signs) and CTCAE grading 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 a window.

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. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind treatment was not administered to the subject. If subjects were re-screened and successfully randomized, then 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 stratum is different to the assigned stratum in IRT, then 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 study epoch. Subjects will be analyzed according to treatment received or actual treatment as described below.

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire induction period, entire maintenance period or entire treatment period.

Protocol deviations for exclusion from analysis populations are defined in Table 2-4.

Table 2-4 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	Mis-randomized subject*
FAS (Full analysis set)	DVSPID: INCL01, OTH20	Mis-randomized subject*
Safety	DVSPID: INCL01, OTH20	Mis-randomized subject*

INCL01: Informed consent missing or not signed prior to initiating study procedures.
OTH20: Severe ICH-GCP non-compliance of study site in the study.

* mis-randomized but re-screened and successfully re-randomized subjects will not be excluded from the analysis set.

2.3 Subgroups of interest

The co-primary endpoint and the key secondary endpoint and selected safety endpoints will be evaluated using the subgroups defined in Table 2-5. Subgroup analyses for the study endpoints are presented in Table 2-6.

Table 2-5 Subgroups definitions

Subgroup variables	Categories	Description	Label for outputs	Suffix for outputs*
Randomization weight strata	body weight stratum (kg:<25, 25-<50, ≥50)		Weight strata	A
Randomization age strata	(<12 years or ≥12 years)		Age strata	B
Previous systemic therapy	Yes, No Failure* (Yes, No)	* at least one therapy with lack of primary efficacy or lack of secondary efficacy or lack of tolerability	Previous systemic therapy	C

*: only for “Previous < systemic > therapy” and embedded subgroup “failure”.

Table 2-6 Subgroup analyses

Endpoint/analysis	Randomization strata including age and weight	Previous psoriasis therapy*
PASI 75/90 response @ Week 12	X	X
IGA mod 2011 0/1 response @ Week 12	X	X
Adverse event	X	

Note: presented are only those endpoints that need subgroup analyses.
*: only for “Previous < systemic > therapy” and embedded subgroup “failure”.

2.4 Patient disposition, demographics and other baseline characteristics

2.4.1 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 by induction period, maintenance period, extension period and follow up period 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. Listing of protocol deviations will be provided along with the relationship to COVID-19.

The patient disposition will be shown for below treatment groups:

- for induction period:
  - AIN457 Low dose, AIN457 High dose, Placebo, Etanercept, Total
- for maintenance period:
  - AIN457 Low dose, AIN457 High dose, Placebo to AIN457 Low dose, Placebo to AIN457 High dose, Etanercept, Total
- for extension period:
  - Any AIN457 low dose, Any AIN457 high dose, Any AIN457 dose
- for follow-up period:
  - AIN457 Low dose, AIN457 High dose, Placebo, Etanercept, Any AIN457 low dose, Any AIN457 high dose, Any AIN457 dose, Total

2.4.2 Demographics and other baseline characteristics

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age (as reported on the eCRF at screening)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (years: <12, ≥12)
- Weight categories (kg: <25, 25-<50, ≥50)
- Gender
- Race
- Ethnicity
- Childbearing potential (for females)

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

Psoriasis specific baseline characteristics and history of disease will be summarized as well: baseline PASI (Psoriasis Area and Severity Index), baseline PASI (≤20, >20), baseline total body surface area (BSA), baseline Novartis Investigator's Global Assessment modified in 2011 (IGA mod 2011 score), psoriatic arthritis (yes, no), time since diagnosis of psoriasis, time since diagnosis of psoriatic arthritis, previous exposure to biologic therapy, previous exposure to systemic psoriasis therapy, previous exposure to non-biologic psoriasis therapy, previous failure to biologic therapy, previous failure to systemic psoriasis therapy, previous failure to non-biologic systemic psoriasis therapy.

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.

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

The background and demographic summary information will be shown for below treatment groups:

- for induction period:

AIN457 Low dose, AIN457 High dose, Placebo, Etanercept, Total

- for maintenance period:

AIN457 Low dose, AIN457 High dose, Placebo to AIN457 Low dose, Placebo to AIN457 High dose, Etanercept, Total

Additional summaries of the background and demographic variables will be performed by IRT dosing error, and by body weight and dose group. See Section 4.1 for details.

2.4.3 Medical history

Any condition entered on the "Medical history" CRF page 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 psoriasis history and other relevant medical history will be provided.

Analyses will be based on the randomized set.

The summaries will be shown for below treatment groups:

- for induction period:

AIN457 Low dose, AIN457 High dose, Placebo, Etanercept, Total

- for maintenance period:

AIN457 Low dose, AIN457 High dose, Placebo to AIN457 Low dose, Placebo to AIN457 High dose, Etanercept, Total

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

2.5.1 Study treatment / compliance

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

The number of secukinumab low dose, secukinumab high dose, etanercept and placebo 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 secukinumab, then it will be assumed that the syringe contained secukinumab. If the medication pack number is not available, then it will be assumed that the secukinumab injection was applied. If this scenario occurs for subjects in the 300 mg treatment group or in the placebo treatment group, respectively, when subjects should receive two identical injections, it will be assumed that they received secukinumab or placebo, respectively, as planned.

The duration of exposure to study treatment will be summarized separately for induction and entire treatment periods by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be displayed. The duration of exposure to study treatment will also be summarized by age strata.

The duration of exposure will be defined as the time from first dose of study medication to the end of treatment period (e.g., maintenance period). 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.

Duration of exposure (days) = min('end of treatment period' date, last dose date + 84 days) - 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 induction period, with the last category "≥12 weeks" as well as for the entire study treatment period.

Additional dose administration listing at weeks 13, 14 and 15 will be created for IRT dosing error affected subjects. Also, subjects who changed dose due to change of weight group will be listed.

2.5.2 Prior, concomitant and post therapies

Medications will be identified using the Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by treatment group for the safety set. Concomitant treatments will be displayed by induction period, maintenance period up to week 52and entire treatment period. For example, medications started in the follow-up periods might be summarized separately.

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 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 visit (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 2-7, but as well for topical, phototherapy and photochemotherapy (yes/no) on randomized set.

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

The analyses of prior and concomitant medications will be based on the safety set.

Table 2-7 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

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The two primary efficacy variables are PASI 75 response at Week 12 and IGA 0 or 1 response at Week 12. The analysis of the co-primary variables will be based on the FAS.

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 full details of the 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 four percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

2.6.1.1 Definition of Psoriasis Area and Severity Index (PASI)

A PASI score (Fredriksson 1978 and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 2-8. The head, trunk, upper limbs and lower limbs will be 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 will be assigned a score of 0-4. The area covered by lesions on each body region will be estimated as a percentage of the total area of that particular body region.

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, thickening, scaling and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 2-8 The PASI scoring system). PASI scores can range from a lowest value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.
Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group.

Table 2-8 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 will 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)

2.6.1.2 Definition of IGA 0 or 1 response

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 2-9. In collaboration with health authorities, in particular the United States Food and Drug Administration (FDA), the IGA mod 2011 scale (see Table 2-9) has been developed based on a previous version of the scale used in secukinumab phase II studies. The only change from the phase II scale to phase III scale was to condense the very severe and severe subjects into one category "severe". The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

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.

The IGA mod 2011 score will be recorded in the CRF.

Table 2-9 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.

Subjects require an IGA mod 2011 score at randomization of 4 in order to participate in the study. Based on this scale, a subject will be considered as IGA 0 or 1 responder if the subject achieves a score of 0 or 1 and improves by at least 2 points on the IGA scale at a given time point compared to baseline.

2.6.2 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-10.

Table 2-10 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Exact Logistic regression	Summary Statistics for continuous data	Time-to-event analysis	Graphs
PASI 75 at Week 12, compared to Placebo	X	X			X
IGA mod 2011 0 or 1 response at Week 12, compared to Placebo	X	X			X
PASI 90 response at Week 12, compared to Placebo	X	X			X

Variable(s)	Summary statistics for binary/ categorical data	Exact Logistic regression	Summary Statistics for continuous data	Time-to-event analysis	Graphs
PASI 50/75/90/100 response over time	X	X			X
IGA mod 2011 0 or 1 response over time	X	X			X
PASI score over time, compared to Placebo			X		X
IGA mod 2011 score over time, compared to Placebo	X				
Change in CDLQI over time up to Week 52			X		
CDLQI 0 or 1 achievement over time, compared to Placebo	X				X
CHAQ score over time			X		
CHAQ response over time	X				
[redacted]					

2.6.3 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 secukinumab (low or high dose) is not superior to placebo in the proportion of subjects with PASI 75 and IGA mod 2011 0 or 1 response at Week 12.

Let p_j denote the proportion of PASI 75 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, 2,

where

- 0 corresponds to placebo,
- 1 corresponds to secukinumab low dose,
- 2 corresponds to secukinumab high dose.

The following hypotheses will be tested

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

H_2: $p_2 - p_0 \leq 0$ versus H_{A2}: $p_2 - p_0 > 0$,

H_3: $r_1 - r_0 \leq 0$ versus H_{A3}: $r_1 - r_0 > 0$,

H_4: $r_2 - r_0 \leq 0$ versus H_{A4}: $r_2 - r_0 > 0$.

In other words:

H_1: secukinumab low dose is not superior to placebo with respect to PASI 75 response at Week 12

H_2: secukinumab high dose is not superior to placebo with respect to PASI 75 response at Week 12

H_3: secukinumab low dose is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

H_4: secukinumab high dose 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 an exact logistic regression model with treatment group, baseline body weight stratum, age stratum and baseline PASI score as explanatory variables (refer to the appendix "5.1.2.2 Exact Logistic regression" for more details).

If exact logistic regression model does not converge, then the following steps will be performed:

- If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with removing continuous covariates (i.e., baseline PASI), followed by removing categorical covariates (i.e., age, bodyweight stratums);
- If convergence not reached at all, then perform Fisher's exact test.

Odds ratios will be computed for comparisons of secukinumab dose regimens versus placebo utilizing the exact logistic regression model fitted. In case of response rates of 0% or 100% in one of the treatment groups, for analyses with multiple imputation, confidence intervals for risk difference and p-values from the t-test for the risk difference comparing to 0 will be provided; for analyses with pure non-responder imputation, Fisher's exact test will be applied and confidence intervals for risk difference will be provided.

2.6.4 Handling of missing values/censoring/discontinuations

The following imputation methods will apply to the missing data for analysis up to Week 52 including primary W12 analysis:

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

- (Pure) Non-responder imputation will be used as a sensitivity method: Missing values with respect to response variables based on PASI score and IGA mod 2011 categories will be imputed with non-response regardless to the reason for missing data. Subjects with missing baseline or those with all post-baseline missing will be imputed with non-response.

2.6.5 Supportive analyses

Sensitivity analyses will be performed as follows: co-primary endpoints (PASI 75 and IGA mod 2011 0 or 1 response at Week 12) and the key secondary endpoint (PASI 90 at Week 12) will be evaluated using the (exact) logistic regression as described in primary analysis method with pure non-responder imputations instead of multiple imputations for missing values.

2.7 Analysis of the key secondary objective

2.7.1 Key secondary endpoint

The secondary variable in testing strategy is the PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 (for superiority comparison of secukinumab doses versus placebo). The PASI 90 response of subjects with severe chronic plaque-type psoriasis at Week 12 will be analyzed in the same way as the primary variables.
The secondary efficacy variable PASI 90 at Week 12, will be analyzed using the FAS unless otherwise specified.

2.7.2 Statistical hypothesis, model, and method of analysis

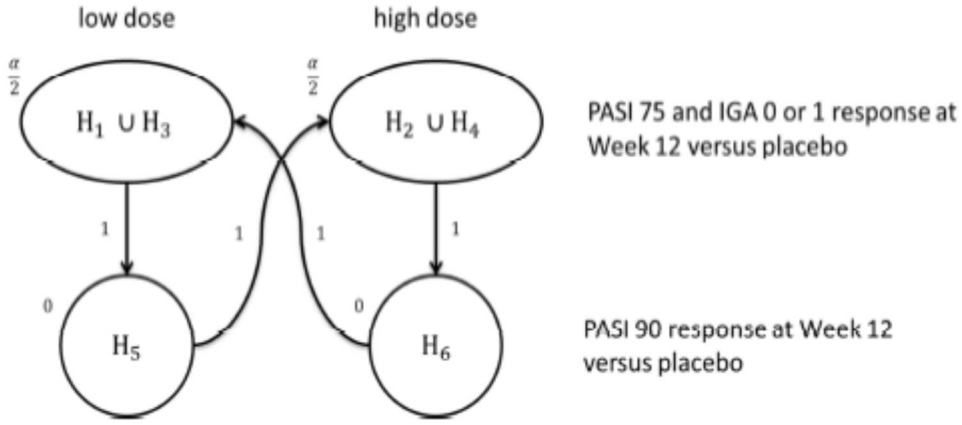
The family-wise type I error will be set to α=2.5% (one-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy. The procedure allows the type I error rate associated with a rejected hypothesis to be reallocated according to a set of pre-specified rules. The hypotheses associated to the primary and secondary variables are as below.

Co-primary variables:
H1 to H4 (see Section 2.6.3)

Secondary variable:

H5: secukinumab low dose is not superior to placebo with respect to PASI 90 response at Week 12
H6: secukinumab high dose is not superior to placebo with respect to PASI 90 response at Week 12
The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy in Figure 2-1.

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 (AIN457) dose regimen. In essence, the type-I-error probability will be equally split for both sets of hypotheses and within each set, the hypothesis will be tested sequentially as follows:

Within each pair, of hypotheses (H1 or H3) and (H2 or H4), each hypothesis is tested at α/2 (one-sided). Only if both hypotheses of a pair are rejected, then the testing sequence will continue.

In the next step of the sequence, the null hypotheses corresponding to the PASI 90 comparison of secukinumab (AIN457) versus placebo will be tested. H5 and H6 will be tested at α/2 (one-sided).
If all hypotheses within a set referring to a secukinumab dose regimen are being rejected, i.e., either (H1, H3 and H5) or (H2, H4 and H6), then the corresponding type I error probability can be passed on to the other set of hypotheses, and if needed, hypotheses can be retested at a higher significance level.

2.7.3 Other Efficacy variables

PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time

Summary statistics for PASI 75, PASI 90, PASI 100 and IGA 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.

For PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response at each visit, each secukinumab dose regimen will be compared to placebo (up to Week 12 only) [redacted] by exact logistic regression with treatment group, baseline bodyweight stratum, age stratum and baseline PASI score as explanatory variables.

For PASI 75, PASI 90 and IGA 0 or 1 response, the placebo-adjusted response rates including 95% confidence interval will be derived by visit up to Week 12. [redacted]

Additional summary analysis will be performed for PASI and IGA response by IRT dosing error and by body weight and dose group. See Section 4.1 for details.

Figures will also be provided.

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.

The IRT dosing error affected subjects will be listed for PASI score.

Percent change from baseline of PASI score (observed cases) will be presented as Spaghetti plot in which the IRT dosing error affected subjects are not shown after Week 12.

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.

The IRT dosing error affected subjects will be listed for IGA mod 2011 score.

[redacted]

[redacted]

CDLQI 0 or 1 achievement
Summary statistics will be provided for number of subjects achieving CDLQI 0 or 1.
Secukinumab groups will be compared to controls (placebo or active) by means of Fisher's exact test. Figures will also be provided.
Additional analysis will be performed for CDLQI results by IRT dosing error. See Section 4.1 for details.

[redacted]

2.7.4 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Analysis of secondary efficacy objective(s)

2.8.1 Secondary endpoints

Same instructions as for primary endpoints.

2.8.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.8.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.9 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.

In general, the following guidelines will be considered for safety analysis:

- Adverse events: Only treatment emergent records are reported in tables, and all AE events will be listed with "treatment emergent" flag displayed.
- Laboratory data (including vital sign and ECG):
  - by period summary statistics tables: only include "on-treatment" records in the tables, i.e., assessments within last dose plus 84 days cutoff. Listings will have the "on-treatment" flag displayed.

In addition to the treatment emergent and on-treatment safety summary, extended entire study period safety analysis may be provided for AE records up to end of study (EOS) and for laboratory by visit summary statistics up to EOS.

Treatment groups for evaluation

The summaries of evaluation will be reported for both induction period and entire treatment period or up to week 24 maintenance period will also be reported, for Week 24 PEA. Treatment period up to week 52 including both induction period and maintenance period will be reported for week 52 analysis. A number of selected safety analyses will be reported for entire study period, which covers the study period from randomization to end of study. The treatment following groups will be used:

- for induction period:
  - AIN457 Low dose, AIN457 High dose, Placebo, Etanercept;
- for maintenance treatment period (or up to week 24/52):
  - by-visit summary: AIN457 Low dose, AIN457 High dose, Placebo to AIN457 Low dose, Placebo to AIN457 High dose, Etanercept, Any AIN457 dose.
  - by-period summary: AIN457 Low dose, AIN457 High dose, Any AIN457 low dose, Any AIN457 high dose, Etanercept, Any AIN457 dose.
- for entire treatment/study period:
  - Any AIN457 low dose, Any AIN457 high dose, Any AIN457 dose, Etanercept*.

*Of note, for subsequent analyses beyond week 52 analysis, Etanercept will only be presented in EAIR

Safety analyses will be performed on treatment received or actual treatment (See Section 2.2: Safety set).

2.9.1 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 2-11.

Only treatment emergent adverse events will be summarized. However all AEs will be included in the listing with flags for treatment emergent. If needed a separate AE listing can be provided to display exclusively AEs with start date later than 84 days since last dose and until EOS.

Treatment emergent adverse events are defined as events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity after dosing based on preferred term and within last dose + 84 days.

Table 2-11 Overview of analyses on some safety endpoints

Analysis Period	AEs & important risks	SAEs & important risks	AEs-SMQ	AEs by severity	study treatment related AEs, death & other significant AEs	Notable (lab/vitals/ ECG)
Induction Period (Day 1 -Week 12)	• crude incidence	• crude Incidence	• crude incidence	• crude incidence	• crude Incidence	• crude incidence
Maintenance Period (up to week 52)	• crude incidence	• crude Incidence	• crude incidence	• crude incidence	• crude Incidence	
Entire treatment	• crude incidence • exp. time adjusted Incidence*	• crude incidence • exp. time adjusted Incidence*	• crude Incidence • exp. time adjusted Incidence*	• crude incidence	• crude Incidence • exp. time adjusted Incidence*	• crude Incidence
Entire study	• exp. time adjusted Incidence*	• exp. time adjusted 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 ≥ 4%, or events that had an incidence rate of at least 5.0 cases per 100 subject-years in one of any treatment group
- Other selected AEs on lower levels (e.g. PT or SMQ level 2), if **appropriate**

Exposure adjusted incidence rates will be also provided for the entire treatment period, by the following subgroups:

- Treatment emergent AEs by SOC, PT and by age strata
- Treatment emergent AEs by SOC, PT and by body weight strata
- Treatment emergent SAEs by SOC, PT and by age strata
- Treatment emergent SAEs by SOC, PT and by body weight strata
- Important identified and potential risks (level 1) based on all adverse events by age strata
- Important identified and potential risks (level 1) based on all adverse events by body weight strata

The crude incidence of treatment emergent adverse events will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in Section 5.1. In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals may be provided.

AEs and serious AEs will be summarized by presenting, for each treatment group (including any AIN457), the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries (crude incidences only) will also be presented for AEs by severity. If a particular AE 'severity' is missing, then 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, then 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, then the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

AEs and SAEs will be presented in terms of exposure time-adjusted incidence rates with 95% confidence intervals for entire study period (up to EOS).

Adverse events will also be summarized 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 grouping term table) will be presented in descending frequency according to its incidence in secukinumab group starting from the most common event. Here, the threshold value z is set to 4 (%) but it may be updated following review of the dry run outputs.

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

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

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

Clinicaltrials.gov and EudraCT

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. Here, the threshold value X is set to 2-5 (%) but it may be updated following review of the dry run outputs.

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 will be 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.

Important identified and potential risks

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 [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. The summary tables for serious cases will not be provided in case of small number of patients.

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.

Analyses by IRT dosing error

Additional analysis will be performed for the treatment emergent adverse events on or after Week 13 visit and up to Day 365, by IRT dosing error, by primary system organ class and preferred term. See Section 4.1 for details.

Adverse events that occurred from Week 13 up to Day 365 since randomization for subjects affected by IRT dosing error will be listed.

2.9.2 Deaths

Separate summary and listing will be provided for deaths.

2.9.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry and urinalysis). All laboratory data will be listed with “on-treatment” flag displayed.

For urinalysis, frequency tables will be presented.

The general guideline for laboratory summaries (hematology and clinical chemistry) is as below:

- All the summary of lab outputs (newly occurring or worsening notables, maximum changes, shift tables, by visit summary statistics) will consider the "on-treatment" data. i.e., all assessments within last dose plus 84 days.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries 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

The laboratory test values below the Lower Level of Quantification (LLQ) or above the Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ values, 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 Table 2-13: 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), estimated glomerular filtration rate (eGFR).

Table 2-13 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
Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L

eGFR	<LLN–60 ml/min/1.73m2	<60–30 ml/min/1.73m2	<30-15 ml/min/1.73m2	<15 ml/min/1.73m2

Note: Per protocol fasting glucose was only required based on glucose urine dipstick result, therefore due to low occurrences it will only be listed and not tabulated.

The number and percentage of subjects with clinically CTCAE grade newly occurring or worsening after baseline (treatment emergent) will be presented. Analysis of hematology CTCAE grades will also be presented by age strata and by body weight strata. Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed. A panel group will be provided to display shift of baseline to minimum evaluation based on CTCAE grades for each hematology parameter (including Leukocytes, neutrophils, lymphocytes and platelets).

2.9.3.1 Liver events

Summaries generated will include:

- Criterion-based "event" tables for selected liver function tests: newly occurring or worsening liver enzyme abnormalities based on the event criteria given in Table 2-14.
- Standard laboratory change from baseline tables of liver function test which are generated by visit. The laboratory tests are listed in Table 2-14.

Listing generated will include overview of liver events; laboratory values of patients with liver events; viral serology, autoimmunity, imaging, pathology, drug abuse of patients with liver events.

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>5x ULN.

Table 2-14 Liver-related events

Parameter	Criterion
ALT	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
AST	>ULN; >3xULN; >5xULN; >8xULN; >10xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN
TBL	>ULN; >1.5xULN, >2xULN
ALP	>ULN;>1.5xULN, >2xULN, >3xULN, >5xULN
ALT or AST & TBL & INR	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 > 3x ULN & INR > 1.5
ALT or AST & TBL & ALP	ALP > 3x ULN & TBL > 2x ULN ALP > 5x ULN & TBL > 2x ULN ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law)** (ALT or AST > 3x ULN & TBL > 2x ULN & ALP < 2x ULN) or reported Hy's Law case

	ALT or AST > 3x ULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))

Liver event will be listed based on ALT and ALP measurements using the closest lab assessment +/- 7 days from the onset of these liver event into the following characteristics 'Hepatocellular' (ALT > 2xULN or ALT/ULN:ALP/ULN > 5), 'Cholestatic' (ALP > 2xULN or ALT/ULN:ALP/ULN ≤ 2), 'Mixed' (ALT > 2xULN and ALP > ULN and 2 < ALT/ULN:ALP/ULN ≤ 5), 'None' (if none of the three above qualifies), and 'Unknown' (in case of a missing ALT or ALP values). Note that the categories are not mutually exclusive.

2.9.3.2 Renal events

Summary table and listing will be presented for "renal event overview". In addition, individual subject data listings will be presented for renal event imaging, pathology, renal function and urinalysis.

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

The following quantitative variables may be summarized if requested: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

Notably abnormal ECG parameters post-baseline will be summarized by computing the number and percentage of subjects with:

- QTcF > 500 msec
- QTcF > 480 msec
- QTcF >450 msec
- QTcF changes from baseline > 30 msec
- QTcF changes from baseline > 60 msec
- PR > 250 msec

A by-subject listing of all quantitative ECG parameters will be provided.

2.9.4.2 Vital signs

Analysis in vital sign measurements 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) by treatment groups for induction, maintenance and extension periods. All vital signs will be listed with "on-treatment" flag displayed.

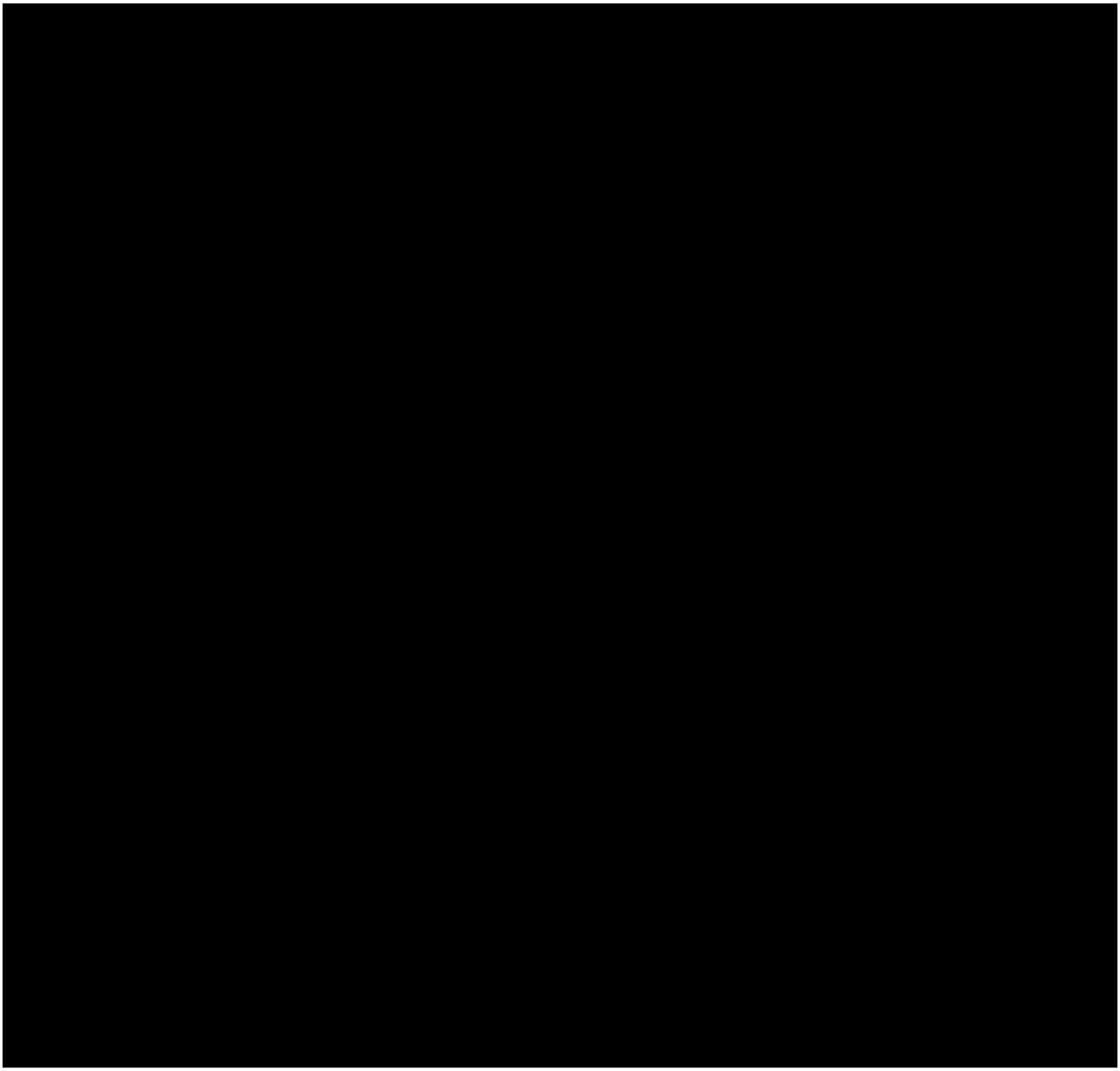
The number and percentage of subjects with newly occurring notable vital signs will be presented for induction, maintenance up to week 52 and entire treatment periods by treatment

group. Subjects not meeting the following criteria at baseline but meeting at post-baseline will be considered to be subjects with newly occurring abnormalities. Criteria for notable vital sign abnormalities are provided in Table 2-15 below.

Table 2-15 Criteria for notable vital sign for pediatric patients

Age group	Systolic BP(mmHg)	Diastolic BP(mmHg)	Pulse (bpm)
6 -11 yrs	90-130	50-80	50-105
12-17 yrs	90-145	55-90	45-95
18 yrs and over	90-140	60-90	60-100

Data of subjects with newly occurring notable vital signs abnormalities will be listed in an additional listing.



2.11 Pharmacogenetics

Not applicable.

2.12 PD and PK/PD analyses

Not applicable.

[redacted]

2.14 Growth and Physical development

Body weight, height and BMI percentile will be summarized by treatment and visit.

Standard height, weight, and BMI curves will be obtained from the U.S. National Center of Health Statistics (www.cdc.gov/growthcharts) curves for ages up to 18 years. These growth curves will be used for all study subjects. The Center's files contain the L, M, and SD parameters needed to generate exact percentiles as follows:

$$z = \frac{\left(\frac{X}{M}\right)^{L} - 1}{L \times SD}$$

where X = physical measurement (e.g., patient's weight, height, and BMI)
M = median
SD= standard deviation
L = the power in the Box-Cox transformation

Percentiles for each patient at each time point will be calculated using the SAS function PROBNORM(z).

The number and percentages of subjects falling in low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95) growth percentiles will be summarized by treatment and visit. Shift from baseline

in growth percentile categories, i.e., low (i.e. <5), normal (i.e. 5-<95), or high (i.e. >= 95), will be summarized by treatment and visit for induction, maintenance and extension period.

2.15 Patient-reported outcomes

The impact of psoriasis on various aspects of subject's health-related quality of life (HRQoL) will be assessed by Children's Dermatology Life Quality Index (CDLQI).
The impact of Psoriatic Arthritis, on those subjects who have reported History of Psoriatic Arthritis will be assessed by their parent/custodian via the use of the childhood health assessment questionnaire, CHAQ©.
Completed questionnaires will be reviewed and examined by the site staff (not the investigator or evaluator of the subject for the physician assessments), before the clinical examination, for responses that may indicate potential AEs or SAEs. If AEs or SAEs are confirmed, then the events will need to be recorded as per instructions given in Section 7 of the protocol.

2.15.1 Children's Quality of Life Index (CDLQI)

The Children's Dermatology Life Quality Index (Lewis-Jones and Finlay, 1995) is a 10-item general dermatology disability index designed to assess health-related quality of life in pediatric subjects aged 4 to 16 years. It is self-explanatory and may be completed by the child with assistance from parents or caregivers as necessary.
The 10 questions cover six areas of daily activities including symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. The questions are based on the preceding week to permit accurate recall.
Each question is answered on a 4-point Likert scale scored from 0 to 3. These are added to give a minimum score of 0 and maximum score of 30. A higher CDLQI score indicated greater degree of QoL impairment. CDLQI is available in two versions, text only and text with cartoons. The text only version will be used in this study. The mean completion time of the text version is 120 seconds. The purpose of the CDLQI in this study is to investigate the effects of treatment of secukinumab with respect to CDLQI at Week 12, compared to placebo, and over time up to Week 52. This questionnaire should be completed in the language the subject is most familiar with before any other clinical assessments. The questionnaire should be completed by the subject with the help of parent/custodian if and as needed. The site staff may help understand the questions, as necessary. The subject should be given sufficient space and time to complete the questionnaire. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses before the clinical examination. The CDLQI questionnaire will be completed by the subject.

For each of the seven scores, the percentage change from baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group. The summary statistics will be presented for subjects till age <18 years and a figure of change from baseline in CDLQI total score over time will be provided. An additional report will be created which will include only CDLQI assessments performed by subjects who were < 16 years of age at time of assessment.

CDLQI 0 or 1 achievement will be also analyzed by visit and over time until week 104 as previously specified in Section 2.7.3.

2.15.2 Childhood Health Assessment Questionnaire (CHAQ) for subjects with Psoriatic Arthritis

The Childhood Health Assessment Questionnaire CHAQ© (Singh et al 1994; Ruperto et al 2001), will be used to assess physical ability and functional status of patients as well as quality of life, for those children only who have reported History of Psoriatic Arthritis. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and other "activities". The person completing the questionnaire (parent/custodian) chooses from four response categories, ranging from 'without any difficulty' to 'unable to do'.

Descriptive statistics will be used to summarize responses on the CHAQ© Questionnaire by treatment, total score and by domain. In case of low number of subjects with completed CHAQ questionnaire, summary statistics of CHAQ and VAS will not be provided.

Parent's or patient's global assessment of patient's overall well-being (VAS)

The parent's or patient's global assessment of patient's overall well-being will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from very well (0 mm) to very poor (100 mm). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

Parent's or patient's assessment of pain (VAS)

The parent's or patient's assessment of pain will be assessed on the VAS that is part of the CHAQ©. The VAS scale ranges from 0-100 mm, from no pain (0 mm) to very severe pain (100 mm). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

For parent's or patient's global assessment of patient's overall well-being and of pain (VAS score) summary statistics for the observed values and the change/percent change from baseline will be provided by visit.

2.15.3 Biomarkers

Not applicable.

2.15.4 Other Exploratory analyses

Not applicable.

2.15.5 Interim analysis

Apart from the final analysis, the study is also planned with two full analyses.

The first full analysis will be performed when all patients completed the Week 24 visit. And the next full analysis will be performed when all patients completed the Week 52 visit (i.e. Maintenance period).

The data cut-off date for the Week 24 PEA is the date of the last Week 24 visit for study subjects, i.e. 7 March 2019. The Week 24 PEA will include all efficacy data up to week 24

visit for each individual subject. For inclusion of safety data, we apply individual data cut-off of each subject to maximize use of available data. Thus for each subject, we will include all safety data collected until the last visit of the subject prior to the PEA data cut-off of 7 March 2019.

The data cut-off date for the Week 52 interim analysis is the date of the last Week 52 visit for study subjects, i.e. 18 September 2019. The Week 52 interim analysis will include all efficacy data up to week 52 visit for each individual subject. For inclusion of safety data, we apply individual data cut-off of each subject to maximize use of available data. Thus for each subject, we will include all safety data collected until the last visit of the subject prior to the interim analysis data cut-off of 18 September 2019.

[redacted]

3 Sample size calculation

Approximately 160 pediatric subjects from 6 to less than 18 years of age, with 2 subgroups: 6 to less than 12 years of age, and 12 to less than 18 years of age. Stratification is planned for age (<12 years, >=12 years) and weight (<25kg, 25-<50kg and >50kg). It will be targeted to have at least 30 subjects in the <12 years subgroup at a minimum. Enrollment of children aged 6 to less than 12 years will proceed after efficacy and safety data for approximately 80 (approximately 40 treated with AIN) enrolled adolescents (aged 12 to less than 18 years) treated for 28 weeks have been reviewed and deemed satisfactory by a Data Monitoring Committee.

Since two secukinumab dose regimens will be tested versus placebo with respect to the coprimary endpoints (PASI 75 response and IGA 0 or 1 response at Week 12), the type-I-error will be split to 1.25% one-sided for each comparison. With 40 subjects per group and assuming a response rate of 10% for PASI 75 response and IGA 0 or 1 response in the placebo group, the power to show a response rate of 65% for PASI 75 response and 45% for IGA 0 response in the secukinumab groups based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions) is approximately 99% for PASI 75 response and approximately 88% for IGA mod 2011 0 or 1 response. For the secondary endpoint of PASI 90 response at week 12, assuming a response rate of 8% in the placebo group, the power to show a significant difference between a secukinumab dose and placebo, assuming a response rate of 39% in the secukinumab groups based on Fisher's exact test (nQuery Advisor 7.0, two group Fisher's-exact test of equal proportions) is approximately 82% for PASI 90 response. The assumed response rates for secukinumab are based on the confirmatory efficacy in severe patients in the adult phase III program. At Week 12, PASI 75 response rates of 11% and PASI 90 response rates of 7% have been reported in the placebo group in Paller et al (2008) for children and adolescents aged 4-17 years.

4 Change to protocol specified analyses

Following are the changes to protocol specific analysis:

Protocol amendment 3 included the plan for an additional Interim Analysis prior to the Week 24 PEA analysis, once sufficient safety [redacted] data had been collected. This analysis aligned with the efficacy extrapolation principle, was expected to provide the basis for a submission package to health authorities (HA), with the intent to allow earlier availability of secukinumab to pediatric patients in countries which accept a submission of clinical data with use of extrapolation methodology. However, due to the acceleration of patient recruitment in the months following the amendment, Novartis concluded that this analysis would no longer bring a considerable time gain for earlier submission. Thus this additional analysis was not performed and the submission of pediatric data will occur according to the initial plan based on the Week 24 PEA.

The following analyses have been removed from the analysis plan:

- The maximum change (maximum decrease and maximum increase) from baseline within treatment period for each laboratory parameter
- The stratified Van- Elteren testing and Hodges-Lehmann estimates for the absolute value and the percentage change from baseline of CDLQI total score.
- "Pure non-responder" imputation will be used, instead of "Modified non-responder" imputation for missing data, as a sensitivity analysis in efficacy analyses.

4.1 Additional and data driven analysis

In addition to the planned analyses, the following additional analyses will be performed after the database lock of the Week 24 analysis.

Analyses using extended visit window for Week 12

Sensitivity analysis with extended Week 12 analysis visit window using MI and pure non-responder imputation for missing data will be performed (Week 12 visit window day 72-102, instead of day 72-88). Number and percentage of subjects with PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response at Week 12 will be summarized. Moreover, an exact logistic regression will be fitted to compare AIN457 low and high dose groups to the controls. This additional analysis was driven by the review of data post Week 24 DBL. As a number of patients, delayed beyond Day 88 their Week 12 CRF visit, this analysis was done to have a better understanding of the impact of these delays.

Analyses by IRT dosing error

In this study, an Interactive Response Technology (IRT) error led to additional dosing of some subjects. The dosing errors happened after the primary endpoint (Week 12) assessment. Specifically, 36 patients who were assigned to the low dose and high dose secukinumab groups were dispensed active medication at Week 13, 14, 15 visits. At these visits, the patients who were randomized to active treatment groups were expected to receive placebo medication as to maintain the blind.

Analyses will be performed for the below groups of IRT error affected and not affected patients to understand the impact of overdosing caused due to the error, by using MI and pure non-responder imputation for missing data:

- AIN457 Low dose Affected
- AIN457 Low dose Not Affected
- AIN457 High dose Affected
- AIN457 High dose Not Affected

Analyses by body weight and dose group

Patients who were randomized to secukinumab treatment arms (low dose and high dose) received secukinumab dose (75 mg, 150 mg or 300 mg) based on the weight categories (<25 kg, 25 to <50kg, ≥50 kg). In addition to the planned secukinumab low dose and secukinumab high dose groups, further analyses will be performed for the below groups by body weight and secukinumab dose:

- AIN457 75 mg and < 25 kg
- AIN457 75 mg and 25-<50 kg
- AIN457 150 mg and 25-<50 kg
- AIN457 150 mg and >=50 kg
- AIN457 300 mg and >=50 kg

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response, the missing data will be imputed by pure non-responder imputation method.

[redacted]

Analyses by IRT dosing error, body weight and dose group

Analyses will be performed for IRT error affected and not affected patients within the groups by body weight and secukinumab dose. The treatment groups will be:

- AIN457 75 mg and 25-<50 kg Not affected
- AIN457 150 mg and 25-<50 kg Affected
- AIN457 150 mg and 25-<50 kg Not affected
- AIN457 150 mg and >=50 kg Affected
- AIN457 150 mg and >=50 kg Not affected
- AIN457 300 mg and >=50 kg Affected
- AIN457 300 mg and >=50 kg Not affected

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response, the missing data will be imputed by pure non-responder imputation method.

Analyses by age strata excluding IRT dose affected subjects

A figure will be provided for PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time, by age stratum, excluding IRT dose affected subjects. Missing data will be imputed by pure non-responder imputation method.

Analyses treating the IRT dose error affected results as missing

Analyses will be performed for PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time, treating the IRT dose error affected results as missing. Frequency and percentage of subjects will be provided, also a figure will be provided.

5 Appendix

5.1 Documentation of statistical methods

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile (Q1), median, upper quartile (Q3), maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

5.1.1 Analysis of continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile (Q1), median, upper quartile (Q3), maximum) will be provided for continuous data by visit and treatment group. For PASI score, CDLQI total scores, summary statistics will be derived for absolute and percentage changes from baseline.

5.1.2 Analysis of binary (and categorical) data

5.1.2.1 Summary statistics for 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 $p > 0$, ($L = 0$ 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 $p < 1$, ($U = 1$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 and PASI 90 response) the placebo-adjusted response rates including exact 95% confidence intervals (using the RISKDIFF option in PROC FREQ) will be derived.

5.1.2.2 Exact Logistic regression

Selected binary outcome variables including PASI 50 / 75 / 90 / 100 response and IGA mod 2011 0 or 1 response, will be evaluated using an exact logistic regression model with treatment regimen, age category, baseline body weight category and baseline score for the response variable. Remove "baseline score for the response variable" from the exact logistic regression model, if model doesn't converge or have insufficient SAS memory issue while executing the model. Odds ratios will be computed for comparisons of secukinumab dose regimens versus control(s) utilizing the exact logistic regression model fitted.

Additional exact logistic analysis will be performed for IRT dosing error subjects, using both multiple imputation and pure non-responder imputed records.

If response rates are 0% or 100% in one of the treatment groups then odds ratio estimates 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 with EXACT statement to calculate the confidence interval for the odds ratios conditional on all other parameters specified in MODEL statement. 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 exact tests in the SAS procedure PROC GENMOD with EXACT statement.

For superiority hypotheses, one sided p-value will be calculated by dividing the two-sided p-value by half (i.e., "p/2") if treatment effect is in favor of secukinumab dose regimens and calculated by "1-p/2" is the treatment effect is in favor of Control.

Exact logistic regression will be applied to response variables at each visit.

If exact logistic regression model does not converge, then the following steps will be performed:

- If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with continuous covariates (i.e., baseline PASI), followed by removing categorical covariates (i.e., age, bodyweight strata);
- If convergence not reached at all, then perform Fisher's exact test.

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

Of note, for the subgroup analysis by body weight or age stratum, the weight stratum or age stratum variable will not be fitted in the exact logistic regression model.

5.1.2.3 Multiple imputations for response variables

PASI 75 and IGA 0 or 1 response at Week 12 will be evaluated using an exact logistic regression model with treatment group baseline body weight stratum, age stratum and

baseline PASI as effects with multiple imputations for missing values. In addition, exact 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.

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.

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

In case of higher drop-out rates or higher study treatment discontinuations for reasons other than lack of efficacy, additional sensitivity analyses will be performed.

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 'PASI score', 'IGA mod 2011 score', 'change from baseline PASI score' and 'change from baseline IGA score' will be imputed simultaneously based on an underlying 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, and number of previous systemic therapies as additional covariates.

The number of imputations will be set to 100, the seed for the random function will be set to 4572310 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 and baseline IGA mod 2011 score as well as all post-baseline IGA and PASI score and all changes from baseline in PASI and IGA scores. Baseline weight and number of previous systemic therapies should also be included in the input data set. Of note, baseline IGA scores will not be considered due to almost all subjects having IGA score = 4.

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi_iga> OUT=<impdata> SEED=457<studycode> NIMPUTE=100 EM converge=1E-2 maxiter=300000;
 <MCMC prior=RIDGE=2;>
 VAR <baseline weight> < >
   <number of previous systemic therapies>
   <baseline PASI> < >
   <change from baseline PASI week1> - <change from baseline PASI week primary endpoint>
   <IGA week 1> - <IGA week primary endpoint>;
BY <treatment group>;
RUN;

ODS LISTING;
```

Programming notes:

- For MCMC option in MI procedure start with <MCMC prior=RIDGE=2;> option. If model converges and no error, then continue with other steps. Otherwise if "prior=RIDGE=2" option does not work then split PROC MI processing into 2 parts, one part with PASI related variables another part with IGA Mod related variables.

  This this approach doesn't work then updated "prior=RIDGE" with "prior=JEFFREYS" option in the above model.
- 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 none missing 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 outcome of interest, i.e. the PASI 75 and IGA 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>=0.75 THEN <PASI 75 response> =1;
ELSE <PASI 75 response>=0;
<…repeat for all PASI response…>

IF <baseline IGA> >=3 THEN DO;
     IF <IGA per week primary endpoint> < 1.5 THEN <IGA 0/1 response> =1;
   ELSE IF <IGA per 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 per week primary endpoint> < 0.5 THEN <IGA 0/1 response> =1;
   ELSE IF <IGA per 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 exact logistic regression and ODDS ratio as described in Section 5.1.2.2. 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 EXACT statement in the GENMOD procedure and the ODS OUTPUT data set "ExactOddsRatio" provides the exact estimate for the odds ratio and confidence intervals.

```
PROC GENMOD <option>;
CLASS <stratum> <treatment>(ref="")/ param=ref;
MODEL <response> = <explanatory variables> / link=logit dist=bin type3;
BY <by-variables);
EXACT <treatment>/  ESTIMATE=both ;
ODS OUTPUT ExactOddsRatio =Estimates;
RUN;
```

The MIANALYZE procedure expects the parameter estimate in the variables ESTIMATE. No standard error estimate for odds ratio will be provided in "Estimates" dataset.

```
Data <modified dataset>;
```

```
  set Estimates;
  ESTIMATE=Estimate;

  if missing(ESTIMATE) then delete;
RUN;
```

The estimates and standard errors of the log (odds ratio) 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 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>;
stderr= stderror;
VARIABLE="estimate";
RUN ;

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

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

In case if exact logistic regression does not converge and risk difference estimates will be provided. The SAS procedure PROC FREQ for risk difference estimates will be applied as follows:

```
ODS LISTING CLOSE;
PROC FREQ DATA=<Imputed dataset> ORDER=DATA;
     TABLES <treatment group>*<response variable>/riskdiff fisher alpha=0.05;
     BY <By-variables>;
     ODS OUTPUT RiskDiffCol1=RiskDiffCol1 FishersExact=fisherexact;
RUN;

ODS LISTING;
DATA DRISK; SET RiskDiffCol1;
     WHERE control="1";
     ESTIMATE=risk;
     STDERR=ase;
     effect="Riskdiff";
```

```
     IF missing(ESTIMATE) OR missing(STDERR) THEN DELETE;
RUN;

PROC SORT DATA=DRISK; BY <By-variables>; RUN;
ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=results VarianceInfo=varinfo ModelInfo=Modelinfo;
PROC MIANALYZE PARAMS=drisk;
     by <By-variables>;
     modeleffects Riskdiff;
     stderr ase;
RUN;

ODS LISTING;
DATA results2;
     set results;
     or=estimate*100;
     lowercl=(LCLmean)*100;
     uppercl=(UCLmean)*100;
     KEEP <response variable> <By-variables> or lowercl uppercl probt;
RUN;
```

5.1.3 Crude incidence and related risk estimates

5.1.3.1 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.

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

5.1.3.3 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.

5.1.3.4 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.

5.1.4 Exposure adjusted incidence rate and related risk estimates

5.1.4.1 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 modelled 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.

[redacted]

5.2 Imputation rules

5.2.1 Study drug

Any partial dates will be imputed as follows: we take the earlier day of:

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

5.2.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, then 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, then 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, then 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.

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

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

1. If AE 'month' is missing, then the imputed AE start date is set to the mid-year point (01JulYYYY).
2. Else if AE 'month' is not missing, then the imputed AE start date is set to the mid-month point (15MONYYYY).

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

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

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

1. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
2. Else if the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
3. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, then 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.

5.2.3 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 days 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, then 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, then 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, then the CM started before treatment. Therefore:
    a. If the CM month is missing, then the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, then the imputed CM start date is set to the midmonth point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, then the CM started after treatment. Therefore:
    a. If the CM month is missing, then 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, then 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, then 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.

5.2.3.1 Prior therapies date imputation

See Section 5.2.3.

5.2.3.2 Post therapies date imputation

See Section 5.2.3.

5.2.4 First diagnosis date (Pso, PsA) imputation

1. If the first diagnosis day/ month are missing and the year is non-missing:

   a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).

   b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).

2. If the first diagnosis day is missing and the month/year are non-missing:

   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 the imputed first diagnosis date is set to the month start point (01MONYYYY).

   b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.2.5 Other imputations

Only PASI and IGA mod 2011 based response variables are imputed with multiple imputation or non-response (see Section 2.6.4), other response variables (e.g. CDLQI 0 or 1 achievement) will be imputed with LOCF.

For CDLQI, CHAQ scores, missing values will be replaced by LOCF. Baseline values will not be carried forward. If no pre-treatment value exists, then 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 (<12 years or >=12 years) and sex, for continuous scale or categorical/ordinal scale, respectively.

The laboratory test values below the Lower Level of Quantification (LLQ) or above the 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 ">")."

5.3 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 [redacted]

5.4 Laboratory parameters derivations

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

See Section 2.2.

5.6 Subject reported outcomes

5.6.1 CDLQI scoring

The scoring of each question is as follows:

- Very much: Scored 3
- A lot: Scored 2
- A little: Scored 1
- Not at all: Scored 0
- Not relevant: Scored 0
- Question unanswered: Scored 0
- Question 7: "prevented school ": Scored 3

The CDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more Quality of Life is impaired.

Meaning of CDLQI Scores

- 0-1= no effect at all on subject's life
- 2-6= small effect on subject's life
- 7-12= moderate effect on subject's life
- 13-18= very large effect on subject's life
- 19-30= extremely large effect on subject's life

The CDLQI will be analyzed under six headings as follows:

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

Interpretation of incorrectly completed questionnaires:

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

1. If one question is left unanswered, then this is scored 0.

2. If two or more questions are left unanswered, then the questionnaire will not be scored.
3. If two or more response options are ticked, the response option with the highest score will be recorded.
4. If there is a response between two tick boxes, the lower of the two score options will be recorded.
5. If one item is missing from a two- item subscale, then that subscale will not be scored.

Handling of missing values:

- If there is only one missing score per visit, it will be imputed with 0, and then the subscale including this item and the total score will be derived accordingly.
- If there are two or more missing scores per visit, then LOCF will be applied to the subscale scores, and total score, separately (i.e. LOCF is NOT applied to the 10 individual question scores for further derivation of the 6 subscale scores and 1 total score).

6 Reference

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