NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2304E1 / NCT01640951
A multicenter, double-blind and open label, 4 year extension study of subcutaneous secukinumab in prefilled syringes, assessing long-term safety, tolerability and efficacy in subjects with moderate to severe chronic plaque-type psoriasis treated with either a fixed dose regimen or on a retreatment at start of relapse regimen

RAP Module 3– Detailed Statistical Methodology Final Analysis

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1.0		First draft (initial) version
Amendment 1.0	11-Apr-18	To correct formatting for bookmarks.

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List of abbreviations

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	body surface area
CHMP	Committee for medicinal products for human use
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DHP	Data Handling Plan
DLQI	Dermatology Life Quality Index
eCRF	electronic case report/record form
FAS	Full analysis set
FDA	United States Food and Drug Administration
HAQ	Health Assessment Questionnaire©
HAQ-DI	Health Assessment Questionnaire© – Disability Index
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA	investigator's global assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IRT	interactive response technology
i.v.	intravenous(ly)
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA Query
PASI	Psoriasis Area and Severity Index
PD	protocol deviation
PDS	Programming Datasets Specifications
PsA	psoriatic arthritis
PT	Preferred Term
RAP	Report and Analysis Plan
RMP	Risk Management Plan

SAE	serious adverse event
SoR	Start of relapse
s.c.	subcutaneous(ly)
SOC	System Organ Class

1 Statistical methods planned in the protocol and determination of sample size

Data will be analyzed by Novartis using SAS according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Statistical and analytical plans

The planned analysis is described in Section 9 (Data Analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR.

This document covers the statistical and analytical plans for the final analysis. All data collected up to end of the study will be analyzed as part of final analysis.

The primary objective of the study is to assess long-term safety and tolerability of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the core studies CAIN457A2304 and CAIN457A2307.

The secondary objectives are:

- To evaluate the long-term efficacy of 150 mg and 300 mg of secukinumab administered at the start of relapse versus fixed interval regimens of 150 mg and 300 mg of secukinumab respectively, in subjects with moderate to severe chronic plaque-type psoriasis who are PASI 75 responders at Week 12, with respect to PASI 75 response:
    - at Weeks 104 and 156, for subjects in the fixed interval regimens, or
    - at Weeks 92 and 144, for subjects in the retreatment at start of relapse regimen who do not require active treatment at Week 92 or 144, respectively, or
    - at Weeks 104 and 156, for subjects in the retreatment at start of relapse regimen who do require active treatment at Week 92 or 144, respectively.
- To evaluate the efficacy of secukinumab treatment regimens in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time.
- To evaluate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque type psoriasis with respect to PASI score and IGA mod 2011 score over time
- To assess the effects of secukinumab treatment regimens with respect to EQ-5D score over time
- To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to changes in DLQI over time
- To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to DLQI 0 or 1 achievement over time
- To investigate the potential development of immunogenicity against secukinumab

- To investigate the occurrence of relapses (achieved maximal PASI improvement from baseline in core study is reduced by >50%) and rebounds in subjects on secukinumab therapy

The exploratory objectives are:

- [redacted]
- To explore the effects of secukinumab with respect to the HAQ-DI in subjects from core study CAIN457A2304 with psoriatic arthritis (PsA) at baseline over time

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

1.1.1 Changes to statistical methods planned in the protocol

Table 1-11 is a modified version of table 6-3 of the protocol to clearly indicate that the area score is derived from area% without rounding.

For the maintenance of response analysis, the non-responder imputation method defined in the protocol will be dropped. The as observed result for PASI and IGA responses will be primarily looked into; the multiple imputation method will be provided as well. Assessment during follow-up period excluded.

In addition to the planned analysis on adverse events, by 1-year interval analysis on the adverse events will be provided in order to assess the occurence of adverse events over time.

1.1.2 Footnotes

Footnotes on outputs will be kept to a minimum also for outputs not covered in [Efficacy MAP M7.1] or [Safety MAP M7.1].

Footnotes will generally be provided for

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

Footnotes will generally NOT be given for

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

1.2 Subjects and treatments

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

Extension Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatments has been assigned and entered the extension study. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization in A2304 and A2307 and thereafter reassigned to treatment at Week 156. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

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

Extension Safety set: The safety set includes all subjects who took at least one dose of study treatment during the extension treatment period. Subjects will be analyzed according to treatment received. The treatment received will be set to the treatment randomized. But if a subject has received the wrong treatment during the entire study, the treatment received will be set to this wrong treatment.

Table 1-1 Subject classification rules

Analysis set	PD Population Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
FAS (Full Analysis Set)	GCP01, GCP06, INCL01, INCL16, INCL18	No post baseline efficacy assessment
Safety	GCP01, GCP06, INCL01, INCL16, INCL18	Not treated in the extension

Note: Protocol Deviation (PD) Populations Codes are available from the study DHP (Data Handling Plan).

Core study A2304: Randomization was stratified by geographical region and by body weight collected at Visit 2 (< 90 kg or ≥90 kg). In study sites selected for psoriatic arthritis assessments according to ACR criteria, randomization was also stratified according to history of psoriatic arthritis at screening.

Subjects were randomized using a 1:1 ratio into one of the treatment groups below:

- **Secukinumab 150 mg group**: AIN457 150 mg s.c. q week x 5 followed by 150 mg s.c. q 4 weeks
- **Secukinumab 300 mg group:** AIN457 300 mg s.c. q week x 5 followed by 300 mg s.c. q 4 weeks

At Week 12 in core study A2304, subjects were classified into 3 categories:

PASI non-responders: were discontinued from study

PASI partial responders: were offered participation into trial CAIN457A2307.

PASI 75 responders: within each dose group (150 or 300 mg s.c.) were re-randomized to one of the two maintenance treatment arms in a ratio of 1:1 (either "fixed interval" or "retreatment at start of relapse") from Week 12 to Week 48.

Thus re-randomization will result to four treatment arms overall in A2304 and also one treatment arm in A2307:

Fixed-time interval regimen – "FI" either 150 or 300 mg s.c. secukinumab: In the maintenance period subjects will receive the same dose they received during the induction period. Thus, secukinumab 150 mg subjects will continue to receive 150 mg secukinumab every four weeks, and secukinumab 300 mg subjects will continue to receive 300 mg secukinumab every four weeks, from week 12 up to and including week 48.

Retreatment at start of relapse regimen – "SOR": "start of relapse" either 150 or 300 mg s.c. secukinumab: "Start of relapse" will be defined as a loss of ≥20% of the maximum PASI gain achieved during the study compared to baseline, *and* a loss of PASI 75 response. Whenever a subject fulfills the start of relapse criteria, active secukinumab will be administered at their scheduled visits (i.e. every four weeks) until the subject is back to PASI 75 response. The dose administered in the maintenance period (secukinumab 150 mg or 300 mg) will be identical to the dose that these subjects received during the induction period. If a subject does not fulfill the criteria of a start of relapse or is back to PASI 75 response after a start of relapse, they will receive placebo injections (two injections per dose) to maintain the blind. This treatment regimen is applied every four weeks, from week 12 up to and including week 48.

Open label (OL) 300 mg s.c. secukinumab: All the partial responders at week 12 in induction period in A2304 will enter A2307 double blind i.v. period (for 8 weeks) and these subjects will be randomized with 1:1 ratio into either "300 mg s.c. secukinumab" or "10 mg per kg i.v. secukinumab". All the subjects will enter open label 300 mg s.c. secukinumab maintenance period from week 8 to week 40.

All the subjects who are eligible from the above 5 treatment groups (4 treatment groups from A2304 and 1 treatment group from A2307) enter the A2304E1 extension study treatment period and continue with same treatment groups. At Week 156, patients under AIN457 150mg FI arm, AIN457 150mg SOR arm, and AIN457 300mg SOR arm could be switched to AIN457 300mg FI arm as determined by physician's judgement.

For the final analysis, data will be presented for the following treatment groups:

- AIN457 150 mg FI
- AIN457 150 mg FI switch to AIN457 300mg FI
- AIN457 150 mg FI combined non-switch and switch
- AIN457 300 mg FI
- AIN457 150 mg SoR non-switched
- AIN457 150mg SoR switch to AIN457 300mg FI
- AIN457 300 mg SoR non-switched
- AIN457 300mg SoR switch to AIN457 300mg FI
- AIN457 300 mg OL
- Any AIN457 300mg
- Any AIN457 150mg
- Any AIN457

Note: any AIN457 300mg (including AIN457 150mg FI switch to AIN457 300mg FI, AIN457 300mg FI, AIN457 150mg SoR switch to AIN457 300mg FI, AIN457 300mg SoR, AIN457 300mg SoR switch to AIN457 300mg FI and AIN457 300mg OL); any AIN 150mg(including AIN457 150mg FI and AIN457 150mg SoR); Any AIN457 including all the groups above.

The following study periods will be considered for analysis:

- **Extension study period**: Week 52 post-dose to Week 268;
- **Entire study period**: Combination of Induction (in A2304 core) period + Maintenance (in A2304 and in A2307) period + Core follow-up period (consider only for subjects who enter E1 after core follow-up period)+ Treatment period in E1 [Initial Randomization in A2304 core to week 268] (including follow-up period);
- **Entire treatment period**: Combination of Induction (in A2304 core) period + Maintenance (in A2304 and in A2307) period + Core follow-up period (consider only for subjects who enter E1 after core follow-up period) + Treatment period in E1 [Initial Randomization in A2304 core to week 260]
- **Follow-up 2 period**: after W268 visit to end of the study.

Table 1-2 Analysis by treatment group

Endpoint/analysis	AIN457 150 mg FI AIN457 150 mg FI switch to 300mg FI AIN457 300 mg FI AIN457 150 mg SoR AIN457 150 mg SoR switch 300 mg FI AIN457 300 mg SoR AIN457 300 mg SoR switch 300 mg FI AIN457 300mg OL	AIN457 150mg FI(NSW+SW)	Any AIN457 150mg Any AIN457 300mg	Any AIN457
Subject disposition	X			X
Demography & baseline characteristics	X			X
Previous & concomitant medication	X			X
Medical history	X			X
Study medication: duration of exposure	X		X	X
Maintanance of PASI 75 response	X			
PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time	X	X		
[redacted]				
PASI score over time	X	X		
IGA mod 2011 score over time	X	X		
Relapse	X			
Rebound	X			
DLQI 0 or 1 achievement	X	X		

Endpoint/analysis	AIN457 150 mg FI AIN457 150 mg FI switch to 300mg FI AIN457 300 mg FI AIN457 150 mg SoR AIN457 150 mg SoR switch 300 mg FI AIN457 300 mg SoR AIN457 300 mg SoR switch 300 mg FI AIN457 300mg OL	AIN457 150mg FI(NSW+SW)	Any AIN457 150mg Any AIN457 300mg	Any AIN457
DLQI	X			
EQ-5D	X			
HAQ©-DI	X	X		
Safety analysis	X		X	X

1.3 Subgroup definitions

No subgroup analysis will be presented in the final analysis. HAQ-DI will be analyzed only for subjects with PsA at Core study entry

1.4 Assessment windows, baseline and post baseline definitions, missing data handling

1.4.1 Assessment windows

No assessment windows have been defined for this study. Visit windows are described below.

If not otherwise specified, 'first dose', 'randomization' and 'baseline' are with respect to core study.

1.4.2 Study Day 1 and other study days

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

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

The descriptor "Day 0" will not be used.

Missing data

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

1.4.3 Screening (core and extension), 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 in core study A2304 (for safety analysis) or prior to the first randomization date (for efficacy analysis) in A2304. Of note, re-randomization will not be used for baseline definition and only one baseline value will be defined referring to the first randomization.

Screening2 refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment **in extension** study A2304E1 (for safety analysis and efficacy analysis).

Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in [PDS].

For efficacy analyses, baseline is the last assessment (including unscheduled visits) obtained before the first randomization in the core study A2304. All assessments obtained after randomization are considered as post-baseline unless otherwise specified.

For safety analyses, baseline is the last assessment (including unscheduled visits) obtained before the first dose of study treatment. All assessments obtained after the first dose of study 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 PROs (e.g. patient's assessment of PsA pain), lab, ECG if no pre-treatment value exists, also a value recorded after first dose can be used as baseline if it was collected on the same day as first dose.

1.4.4 Visits windows

Visit- windows will be used for the data that is summarized by analysis visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 1-8

. In this table, the days are counted since the first dose of study treatment (study days) for safety assessments, and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, 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 1-8 Assessment windows for scheduled visits

Analysis Visit	**Week** (relative to baseline of core)	**Scheduled Day**	**Visit Window**
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
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
Ext1 Week 52 / Screening 2	52	365	Day 352-379
Week 56	56	393	Day 380-407
Week 60	60	421	Day 408-435
Week 64	64	449	Day 436-463
Week 68	68	477	Day 464-491
Week 72	72	505	Day 492-519
Week 76	76	533	Day 520-547
Week 80	80	561	Day 548-575
Week 84	84	589	Day 576-603
Week 88	88	617	Day 604-631
Week 92	92	645	Day 632-659
Week 96	96	673	Day 660-687
Week 100	100	701	Day 688-715
Week 104	104	729	Day 716-743
Week 108	108	757	Day 744-771
Week 112	112	785	Day 772-799

Week 116	116	813	Day 800-827
Week 120	120	841	Day 828-855
Week 124	124	869	Day 856-883
Week 128	128	897	Day 884-911
Week 132	132	925	Day 912-939
Week 136	136	953	Day 940-967
Week 140	140	981	Day 968-995
Week 144	144	1009	Day 996-1023
Week 148	148	1037	Day 1024-1051
Week 152	152	1065	Day 1052-1079
Week 156	156	1093	Day 1080-1107
For AIN457 300mg FI/AIN457 300mg SoR switch to AIN457 300mg FI/AIN457 150mg FI/AIN457 150mg FI switch to AIN457 300mg FI/AIN457150mg SoR switch to AIN457 300mg FI			
Week 168	168	1177	Day 1108-1219
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 1584-1667
Week 244	244	1709	Day 1668-1765
Week 260	260	1821	Day 1766-1835
Week 264	264	1849	Day 1836 – 1863
Week 268	268	1877	Day 1864 - 1891
For AIN457 300mg SoR/AIN457 150mg SoR			
Week 160	160	1121	Day 1108-1135
Week 164	164	1149	Day 1136-1163
Week 168	168	1177	Day 1164-1191
Week 172	172	1205	Day 1192-1219
Week 176	176	1233	Day 1220-1247
Week 180	180	1261	Day 1248-1275
Week 184	184	1289	Day 1276-1303
Week 188	188	1317	Day 1304-1331
Week 192	192	1345	Day 1332-1359
Week 196	196	1373	Day 1360-1387
Week 200	200	1401	Day 1388-1415
Week 204	204	1429	Day 1416-1443
Week 208	208	1457	Day 1444-1471
Week 212	212	1485	Day 1472-1499

Week 216	216	1513	Day 1500-1527
Week 220	220	1541	Day 1528-1555
Week 224	224	1569	Day 1556-1583
Week 228	228	1597	Day 1584-1611
Week 232	232	1625	Day 1612-1639
Week 236	236	1653	Day 1640-1667
Week 240	240	1681	Day 1668-1695
Week 244	244	1709	Day 1696-1723
Week 248	248	1737	Day 1724-1751
Week 252	252	1765	Day 1752-1779
Week 256	256	1793	Day 1780-1807
Week 260	260	1821	Day 1808-1835
Week 264	264	1849	Day 1836 – 1863
Week 268	268	1877	Day 1864 - 1891

* Baseline measurement before the first drug administration for safety assessments and before the first randomization in CAIN457A2304 for efficacy assessments. The days are counted since the first dose of study treatment for safety assessments, and the days are counted since the date of randomization for efficacy assessments.

For parameters which are not collected at every visit (e.g. weight, DLQI, EQ-5D, HAQ-DI), visit windows defined in the tables above will be combined. E.g., if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 100 to Day 183 (combining Week 13 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 1.4.5 below 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, it would not be mapped for the analysis.

1.4.5 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 1-8 & Table 1-9).

For baseline assessment definition see Section 1.4.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),

- in case qualitative variables are based on quantitative variables, e.g. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 1-9 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 1.4.3
Post-baseline efficacy	All data except DLQI, EQ-5D and health assessment	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used.
Post-baseline efficacy	DLQI, EQ-5D and health assessment	The measurement closest to the target day will be used. In the event two measurements are taken equally apart the earlier one will be used. If two measurements have been taken on the same day, select the worst.
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same date/different time then select the first one(using the time); If two measurements are taken on the same date/time/different visit number then use the first visit number (assuming this is the planned visit); If two measurements are taken on the same date/time/CRF visit then take the average value
Post-baseline safety	Notable abnormalities (e.g., vital signs, ECG), CTCAE grades	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 (analysis period).

1.4.6 Day of last dose of 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 including follow-up 1 period or the last dose date +84 days which happened earlier.

1.5 Subject disposition, background and demographic characteristics

1.5.1 Subject disposition

The number and percentage of subjects in the randomized set who entered and completed study periods), and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group. The reason for patients discontinuation from study treatment will be presented by yearly interval (analysis visit) for AIN457 150 mg (switch+non-switch) and AIN457 300 mg.

1.5.2 Background and demographic characteristics

The following common background and demographic variables from **core** study will be analyzed for assessing the baseline comparability:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI)

Categorical variables:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Gender
- Race
- Ethnicity
- Smoking status

Psoriasis specific baseline characteristics and history of disease will be summarized as well: Baseline PASI score , baseline PASI (<=20, >20), baseline total BSA baseline IGA mod 2011 score (at least mild, moderate, severe), Severity of psoriasis, presence of psoriatic arthritis (yes, no), types of previous psoriasis therapies, time since diagnosis of psoriasis, time since diagnosis of psoriatic arthritis, previous exposure to biologic systemic psoriasis therapy, previous exposure to systemic psoriasis therapy, previous exposure to non-biologic systemic psoriasis therapy, previous failure to biologic systemic psoriasis therapy, previous failure to systemic psoriasis therapy, previous failure to non-biologic systemic psoriasis therapy.

Previous psoriasis therapy will be combined from previous psoriasis therapy recorded in CORE study and also concomitant medications entered in EXTENSION study which started on or prior to the inform consent date of CORE study. The ATC code is defined in PDS.

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

BMI = (body weight in kilograms) / (height in meters)^2

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

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the FAS. 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 FAS.

Unless otherwise specified, analyses will be based on the FAS.

1.5.3 Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term. Psoriasis specific medical history will be summarized by treatment group. Previous treatments for psoriasis and whether or not response was achieved will be summarized by treatment group.

The medical history information combines the medical history data collected in CORE study and also data entered in AE domain in the extension study which started on or prior to screening

1.6 Study medication

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

The number of planed and actual injection number will be summarized by yearly interval (analysis visit) for entire treatment period and treatment group AIN457 150 mg FI and AIN457 300 mg FI.

In case it cannot be identified from the data collected or assumed from the planned treatment whether an injection contained placebo or secukinumab, it will be assumed that the syringe contained secukinumab. For example this applies to the 150 mg secukinumab treatment group (in which subjects should receive both an active and a placebo injection) if only one injection is given. If the medication pack number is not available, it will be assumed that the secukinumab injection was applied. If this scenario occurs for subjects in the 300 mg treatment group when subjects should receive two identical injections, it will be assumed that they received secukinumab as planned.

The duration of exposure to study drug will be summarized by treatment group and yearly interval for entire treatment period.

Duration of exposure will be defined and summarized as follows:

For extension study period, duration of exposure will be defined as the time from first dose of study medication in extension 1 to the end of treatment period in extension 1 study; and for entire study period duration of exposure will be defined as the time from first dose of study medication in core study to the end of treatment period in extension 1 study. 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 study visit date, last dose date + 84 days) - first dose date + 1

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

Duration of exposure (100-patient years) = duration of exposure (years) / 100

The analyses of duration of exposure described above will be done for the extension study period and for the entire study period.

1.7 Concomitant medication

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.

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 vist (including follow-up visits) whichever occurs earlier will be a **concomitant** medication, including those which were started pre-baseline and continued into the treatment period.

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

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

Listings of prior or concomitant medication during entire study period and follow-up 2 period will be provided separately.

1.8 Efficacy evaluation

1.8.1 Variables

The primary objective of the study is to assess long-term safety and tolerability of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the core studies CAIN457A2304 and CAIN457A2307.

The analysis of the secondary efficacy variables will be based on the FAS.

The main secondary efficacy analysis is maintenance of response. Maintenance of response is defined as follows:

- for subjects in the fixed interval regimens, maintenance of response is defined as PASI 75 response at Weeks 104 and 156
- for subjects in the start of relapse regimens maintenance of response is defined as

- PASI 75 response at Weeks 92 and 144 for subjects who do not require active treatment at Week 92 or 144 and
- PASI 75 response at Weeks 104 and 156 for subjects who do require active treatment at Week 92 or 144.

In order to identify whether active treatment was applied at Weeks 92 and 144 the following will be utilized:

- Visit windows as in Table 1-8 (as for efficacy with date of randomization as day 1) will be applied to dosing date.
- The analysis visit Weeks 92 and 144 will be identified for dosing. The PASI assessment for the corresponding CRF visit will be selected.
- If no dosing for analysis visit Weeks 92 and 144 is identified, it is concluded that no active treatment was given. Therefore, the PASI 75 response status of the analysis visit Weeks 92 and 144 will be considered.
- For subjects with assigned dosing records at Weeks 92 and 144 but for which no corresponding PASI assessment can be assigned, non-responder imputation will be performed

Apply visit windowing to the dosing dates then find the weeks 92 and 144 dosing date. With this dosing date search for the corresponding PASI data with the same date. If there was no AIN dosing at these weeks 92 and 144 then it shall be assumed that the PASI response at Weeks 92 and 144 will be taken for the maintenance of response parameter.

Table 1-10 lists the variables for the final analysis.

Table 1-10 Primary, secondary and exploratory variables

Variable	Type
Long term safety and tolerability of secukinumab	Primary
Maintenance of response	Secondary
PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time	Secondary
PASI score over time	Secondary
IGA mod 2011 score over time	Secondary
Start of relapse	Secondary
Time to relapse	Secondary
Rebound	Secondary
DLQI 0 or 1 achievement	Secondary
EQ-5D	Secondary
DLQI	Secondary
HAQ-DI score over time1	Exploratory

Variable	Type
HAQ-DI response over time[1]	Exploratory
[redacted]	[redacted]

[1]only for subjects with psoriatic arthritis (PsA) at baseline of core study

1.8.1.1 Definition of PASI and related variables

The total BSA affected by plaque-type psoriasis was estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations were done: each reported percentage was multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 1-11.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) was derived as indicated in Table 1-11. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

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

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

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

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 1-11).

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

The investigator was only responsible for collecting the components or scoring signs and total regional area. PASI calculations were done via the PASI Score eCRF.

The PASI scores calculated via the PASI Score eCRF will be used in the analysis and for derivation of PASI response values, relapse and rebound (see below).

Table 1-11 The PASI scoring system

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

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

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

- **PASI 50 response**: subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders
- **PASI 75 response**: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders

- **PASI 100 response**: complete clearing of psoriasis (PASI=0)

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

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 1-12) has been developed based on a previous version of the scale used in secukinumab phase II studies, and has been updated in collaboration with health authorities (in particular the FDA.).The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points.

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

Table 1-12 The IGA mod 2011 rating scale

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

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

Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA scale compared to baseline.

1.8.1.2 Health Assessment Questionnaire - Disability Index (HAQ-DI)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ (Health Assessment Questionnaire – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty [1], much difficulty [2], and unable to do [3].

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

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

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

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

HAQ-DI response is defined by an improvement of at least 0.3 score points compared to baseline.

Table 1-13 Companion aids/devices items for HAQ-DI categories

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

1.8.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 1-14

Table 1-14 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Summary statistics for continuous data	Graphs
Maintenance of response	X		
PASI 50/75/90/100 response over time	X		X
[redacted]			
Absolute PASI score over time		X	
Absolute change and % change PASI over time		X	
IGA mod 2011 0 or 1 response over time	X		X
IGA mod 2011 score over time		X	
Relapse	X		
Rebound	X		
EQ-5D	X	X	
Absolute DLQI		X	
% change DLQI		X	
DLQI 0 or 1 achievement	X		
HAQ-DI score over time		X[1]	
HAQ-DI response over time	X[1]		

[1]only for subjects with psoriatic arthritis (PsA) at baseline of core study

1.8.2 Statistical hypothesis, model, and method of analysis

Not applicable.

1.8.3 Testing strategy

No formal hypothesis testing will be performed for this extension study.

1.8.4 Handling of missing values/censoring/discontinuations

As observed value (Follow-up assessment excluded) will be reported primarily for both efficacy and PROs.

Response variables based on PASI score and IGA mod 2011 categories will be imputed with multiple imputation (MI) (Follow-up assessment excluded) as secondary analysis method. Summary tables for PASI scores and IGA mod 2011 categories will also be imputed using MI. Other response variables (e.g. DLQI 0 or 1 achievement) will be imputed with LOCF (Follow-up assessment excluded).

1.8.4.1 Multiple imputations for response

The number of imputations will be set to 100 the seed for the random function will be set to 4572304 for this study.

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 change from baseline or IGA mod 2011 categories will be imputed separately 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.

Of note: subjects with missing baseline or subjects with all post-baseline missing will be included in the multiple imputation analysis.

1.8.5 Supportive analyses

Not applicable.

1.8.6 Secondary variables

1.8.7 Methods of analysis

Maintenance of response

Maintenance of response is defined as follows:

- for subjects in the fixed interval regimens, maintenance of response is defined as PASI 75 response at Weeks 104 and 156
- for subjects in the start of relapse regimens maintenance of response is defined as

- PASI 75 response at Weeks 92 and 144 for subjects who do not require active treatment at Week 92 or 144 and
- PASI 75 response at Weeks 104 and 156 for subjects who do require active treatment at Week 92 or 144.

Summary statistics of Maintenance of response will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time

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

PASI score over time

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

IGA mod 2011 score over time

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

Relapse

The number and percentage of subjects experience relapse will be presented by treatment group and visit.

Rebound or rebound like events

The number and percentage of subjects experiencing rebound or rebound like events will be presented by treatment group as follows:

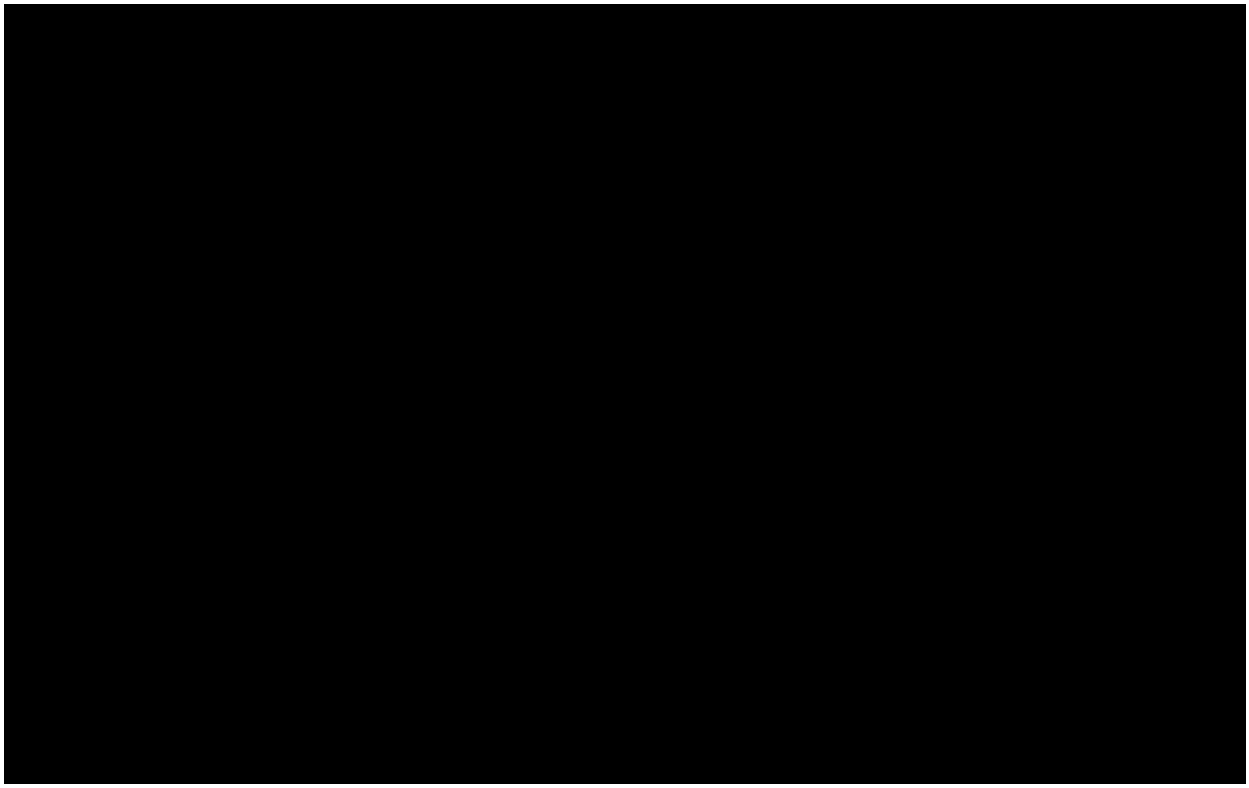
- For rebound, all assessments done up to 8 weeks after last injection will be summarized.
- Similarly for rebound like events, all assessments done up to 12 weeks after last injection will be summarized.

  Subjects who received commercially available Cosentyx® will be excluded from this analysis.

1.8.8 Exploratory analyses

Psoriatic arthritis

Summary statistics will be provided for HAQ-DI score and HAQ-DI response over time for all subjects with psoriatic arthritis recorded on the Psoriatic Arthritis History eCRF at screening.



1.8.9 Biomarkers

Not applicable.

1.8.10 Health-related Quality of Life (HRQoL)

Summaries will be based on the FAS and will be presented separately for study periods if not specified otherwise.

Dermatology Life Quality Index

The DLQI measures functional disability of subjects with dermatological disorders that are greater than 18 years of age and had been utilized as a relevant clinical measure in atopic dermatitis, as well as other dermatitis clinical trials. The DLQI is a simple, validated, self-administered 10-item questionnaire. The instrument contains six functional scales (i.e., symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). For the DLQI, each question will be answered with the following response: “not at all,” “a little,” “a lot,” or “very much”. Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1.

Output shells in MAP module 7.1: T_DLQIANA3

EQ-5D

The EQ-5D is a questionnaire with 5 questions each with three categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of subjects in each of the three categories for each question will be presented by analysis visit and treatment group.

Summary statistics will be shown for the health state assessment by analysis visit and treatment group.

HAQ©-DI (for subjects with PSA at baseline of the core study)

Summary statistics will be derived for HAQ©-DI score over time for all subjects with psoriatic arthritis recorded on the Psoriatic Arthritis History eCRF at screening visit of the core study.

Absolute and relative frequencies for HAQ©-DI response will also be presented. HAQ©-DI response is defined by an improvement of 0.3 score points compared to baseline.

1.9 Standard safety evaluation

All safety analyses will be based on the safety set. Core study baseline will be used for all change from baseline analysis.

Absolute and relative frequencies and exposure time adjusted incidence rate or event rate analysis will consider all the events (AEs/SAEs and clinically significant newly occurring lab, vitals and ECG abnormalities) that occurred in core studies and extension study for entire treatment period and in extension study for treatment period in E1.

Safety analyses will be performed on treatment received or actual treatment (See Section 1.2).

1.9.1 Adverse events

Treatment emergent adverse are defined as events started after the first dose of study medication or events present prior to the first dose of study medication but increased in severity after dosing based on preferred term and within last dose + 84 days or last visit date of follow-up 1 period which comes earlier. Only treatment emergent adverse events are summarized

The crude incidence of treatment emergent adverse events will be presented for the entire treatment period and also by yearly interval (365 days) for 150 and 300 mg FI cohorts. The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived as described in Section 2.3.1. In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided for the entire treatment period by yearly interval (365 days) for 150 and 300 mg FI cohorts.

Please note that exposure adjusted incidence rates will be provided and follow the guideline as below:

- Primary SOC level for AE and SAE
- Level 1 for risks and SMQ

- PT level for SAE
- PT level for AE ≥ 2%, or events that had an incidence rate of at least 5.0 cases per 100 subject-years in one of any AIN457 XXX mg
- Other selected AEs on lower levels (e.g. PT or SMQ level 2), if appropriate
- Special AE interest:
-

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

Adverse events will be summarized by presenting, for each treatment group (including "any AIN457"), the number and percentage of subjects having at least one AE at each year interval (for 150 and 300 mg FI cohorts), having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT or ≥ z % in any group for each SMQ table) will be presented in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event. Here threshold value z is set to 1 (%) but it may be updated following review of the dry run outputs.

Adverse events that started in core studies before the first dose of the study treatment in extension and continued into extension will not be included in the on treatment in E1 tables. Separate summaries will be provided for deaths, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

Adverse events will also be summarized by SMQ according to MedDRA.

Exposure time will be derived as following:

- Starting day: is the first study day of each period (Day 1 for year 1, Day 366 for year 1-2, etc.,)
- Ending day:
    - For patients with events: first AE onset day within each interval (worsening is not considered between the yearly interval) or first lab event assessment day
    - For patients without any event during the interval:
        i. Censored day for AEs is defined as min [end of period day (i.e., day 365 for year 1, day 730 for year 1-2, etc.,), or min(last visit day, last dose + 84 days) for early discontinued subjects, or switched date]
        ii. Censored day for Labs will be end of period day (i.e, day 365 for year1, day 730 for year 1-2, etc.,) for ongoing patients or the last assessment day within each interval.

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

listings of all adverse events will be done based on entire study period and follow-up 2 period separately. A column indicating if the adverse event is treatment emergent or not will be shown. Non-treatment emergent adverse events may be summarized separately upon request.

Algorithms for date imputations will be provided in RAP M8.

1.9.2 Laboratory data

All the summaries of lab data (newly occurring notables, shift tables, by visit summaries, maximum changes if required) will only include data during treatment period, which are defined as those lab assessments within last dose plus 84 days or last visit of follow up period which comes earlier.

The laboratory values below Lower Level Of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ, 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 ">")."

All the listings of lab data will include all records with an on-treatment flag, i.e., a yes-or-no flag indicating whether the record occurred within last dose plus 84 days.

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology, clinical chemistry and urinalysis). In addition to the individual laboratory parameters, the ratios "total cholesterol / HDL" and "apolipoprotein B / apolipoprotein A1" will be derived and summarized.

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

change from baseline = post baseline value – baseline value

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline will be analyzed analogously.

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 the treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 1-18: 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), glucose, cholesterol, triglycerides (TG).

The number and percentage of subjects with clinically CTCAE grade newly occurring or worsening after baseline will be presented for the treatment period.

Absolute and relative frequencies will be derived for non-overlap groups: CTCAE grade 1, CTCAE grade 2, CTCAE grade 3, and CTCAE grade 4; and exposure adjusted incidence rate will be derived for nesting groups: CTCAE grade >=1, CTCAE grade >=2, CTCAE grade >=3, CTCAE grade 4.

Table 1-18 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN - 6.2 mmol/L	<6.2 - 4.9 mmol/L	<4.9 mmol/L	
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*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >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
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

*Note: for “creatinine increased” the baseline criteria do not apply

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase (either initial or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in the core study. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

Exposure adjusted incidence rate for neutropenia CTCAE grade >= 2 will be presented for the entire treatment period.

Summaries for newly occurring or worsening clinically notable lipid abnormalities will also be provided cumulatively for each of the following parameters and categories:

- HDL:
  - <=LLN
  - <0.8 x LLN
- LDL, cholesterol, triglycerides:
  - >=ULN
  - >1.5 x ULN
  - >2.5 x ULN

Subjects with newly occurring or worsening after baseline abnormalities in lipid parameters will be listed. If a subject experiences newly occurring or worsening of abnormality for a parameter the entire time course of that parameter will be listed.

Newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 1-19.

Table 1-19 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
TBL	>1xULN; >1.5xULN; >2xULN; >3xULN,
ALP	>1.5xULN; >2xULN; >3xULN; >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >1.5xULN; ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN ALT or AST >20xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP ≤2xULN **(Potential Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP >2xULN may not result in severe DILI.

Notes:
1) In studies which enroll subjects with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria
2) In case an Adjudication Committee is in place it may be meaningful to summarize all abnormalities classed as e.g., *definitely/probably* (depending on the categories used) related to study treatment

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.

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

1.9.3 Vital signs

All the summaries of vital signs will only include data during treatment period, which are defined as those lab assessments within last dose plus 84 days or last visit of follow up period which comes earlier.

All the listings of vital signs will include all records with an on-treatment flag, i.e., a yes-or-no flag indicating whether the record occurred within last dose plus 84 days.

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group.

Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of subjects with newly occurring notable vital signs will be presented. Clinically notable vital sign results are provided in Table 1-20 below. The crude incidence for the treatment period will be shown for entire treatment period.

Table 1-20 Criteria for notable vital sign abnormalities

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

1.9.4 Electrocardiogram (ECG)

All the summaries of ECG will only include data during treatment period, which are defined as those lab assessments within last dose plus 84 days or last visit of follow up period which comes earlier.

All the listings of ECG will include all records with an on-treatment flag, i.e., a yes-or-no flag indicating whether the record occurred within last dose plus 84 days.

The following quantitative variables will be summarized: 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.

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

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

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

In addition, shift tables comparing baseline ECG results (normal, abnormal, not available, total) with the maximum on-study result (normal, abnormal, not available, total) will be provided.

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

1.9.5 Immunogenicity

A listing of immunogenicity data will be provided.

1.10 Sample size calculation

Not applicable.

1.11 Power for analysis of key secondary variables

Not applicable.

1.12 Interim analyses

Four interim analyses have been done, first one at the time of 120 days safety update; second one for 3 years IA; third one for 4 years IA; and one for 5 years IA.

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Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum.

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

2.1 Analysis of continuous data

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

2.2 Analysis of binary (and categorical) data

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

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

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

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

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

2.2.2 Multiple imputations for response variables

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

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

The number of imputations will be set to 100, the seed for the random function will be set to 4572304 for this study. To generate the multiple imputed data sets, the SAS procedure MI can be used as follows:

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

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

Programming notes:

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

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

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

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

2.3 Crude incidence and related risk estimates

2.3.1 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.

2.4 Exposure adjusted incidence rate and related risk estimates

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

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

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

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

2.5 Subject reported outcomes

2.5.1 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item general dermatology disability index designed to assess Health-related quality of life in adult subjects with skin diseases (e.g. psoriasis). The measure is self-administered and includes six domains of symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment.

The scoring of each question is as follows:

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

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

Meaning of DLQI Scores:

- 0-1= no effect at all on subject's life
- 2-5= small effect on subject's life
- 6-10= moderate effect on subject's life
- 11-20= very large effect on subject's life
- 21-30= extremely large effect on subject's life

The DLQI will be analyzed under six headings as follows:

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

Interpretation of incorrectly completed questionnaires:

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

1. If one question is left unanswered this is scored 0.
2. If two or more questions are left unanswered the questionnaire will not be scored.
3. If question 7 is answered 'yes' this will be scored 3. If question 7 will be answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this will then be scored 2 or 1, respectively.
4. If two or more response options are ticked, the response option with the highest score will be recorded.
5. If there is a response between two tick boxes, the lower of the two score options will be recorded.
6. If one item is missing from a two- item subscale 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 are derived accordingly.
- If there are two or more missing scores per visit, LOCF will be applied to the individual question scores, 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).

Of note, in situations where subjects responded to more questions than what was expected or required, the “most severe” answer was entered into the WriteResult (vendor for PRO data) database. In most cases the Self-Evident Corrections (SECs) were defined correctly, however, the SEC regarding question 7A/7B was not designed to select the “most severe” answer. This was confirmed with Novartis HEOR and communicated to the AIN team.

2.5.2 EQ-5D

The EQ-5D is a generic instrument developed by the EuroQoL group to assess subject’s health status for clinical and economic appraisal. The instrument essentially consists of two pages – the EQ-5D descriptive system and the EQ visual analogue scale (VAS). The EQ-5D descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Each dimension has three response levels: no problems, some problems, severe problem. The subject is asked to indicate the subject’s health state by ticking in the box against the most appropriate statement in each of the five dimensions.

The VAS records the respondent’s self-rated health on a vertical 20-cm visual analogue scale where the endpoints are labeled ‘Best imaginable health state’ and ‘Worst imaginable health state’. Health Assessment Questionnaire - Disability Index (HAQ-DI)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University. The disability assessment component of the HAQ, the HAQ-DI (Health Assessment Questionnaire – Disability Index), assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty [1], much difficulty [2], and unable to do [3].

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

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if **any** "aids or devices" and/or "help from another person" items at the bottom of each page are checked with the exception of "other", the category to which they apply will be adjusted upward to "2". If the basic score is **already** "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can **only** change a category's score to "2"; they do **not** change the score to a "1" or a "3". Companion aids/devices items for HAQ-DI categories are presented in Table 2-2 Companion aids/devices items for HAQ-DI categories

. No score will be adjusted for "other" ticked, regardless of the "other" specification.

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

HAQ-DI response is defined by an improvement of at least 0.3 score points compared to baseline.

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

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

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