NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A2302E1 / NCT01544595

A multicenter, double-blind, randomized withdrawal extension study of subcutaneous secukinumab in prefilled syringes to demonstrate long-term efficacy, safety and tolerability up to 4 years in subjects with moderate to severe chronic plaque-type psoriasis completing preceding psoriasis phase III studies with secukinumab

RAP Module 3 – Detailed Statistical Methodology for final analysis

Author: [redacted]

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1.0	15-Sep-2017	Final
Amendment 1.0	25-Oct-2017	Amylase and Lipase related criateria added in table 1-18

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AE	adverse event
ALQ	above level of quantification
ALP	alkaline phosphatase
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANCOVA	analysis of covariance
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BLQ	below level of quantification
BMI	Body Mass Index
BSA	body surface area
CHMP	Committee for medicinal products for human use
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CSA	cyclosporine A
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHP	Data Handling Plan
DLQI	Dermatology Life Quality Index
DNA	Deoxyribo Nucleic Acid
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	electronic case report/record form
EQ-5D	EuroQOL 5-Dimension Health Questionnaire©
FAS	full analysis set
FDA	United States Food and Drug Administration
GGT	gamma-glutamyl transferase
HAQ	Health Assessment Questionnaire©
HAQ-DI	Health Assessment Questionnaire© – Disability Index
HDL	high density lipoprotein

Hgb	Hemoglobin
HRQoL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
IA&R	Integrated Analytics & Reporting
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDF	International Diabetes Federation
IEC	independent ethics committee
IGA	investigator's global assessment
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
IIS	Integrated Information Sciences
IRT	interactive response technology
i.v.	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low density lipoprotein
LLN	Lower Limit of Normal
MACE	Major Adverse Cardiovascular Event
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PBO	Placebo
PD	pharmacodynamic(s)
PD	protocol deviation
PEA	Primary end point analysis
PG	pharmacogenetic(s)
PGIC	Patient Global Impression of Change
PhGA	physician global assessment
PtGA	patient's global assessment
PK	pharmacokinetic(s)

PsA	psoriatic arthritis
PT	Preferred Term
PUVA	psoralen + UVA treatment
QFT	QuantiFERON TB-Gold test
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
REB	research ethics board
RMP	Risk Management Plan
RW	Randomized withdrawal period
SAE	serious adverse event
SDI	Standard Disability Index
SPP	Safety Profiling Plan
s.c.	subcutaneous(ly)
SOC	System Organ Class
TB	Tuberculosis
TBL	total bilirubin
TG	Triglycerides
ULN	Upper Limit of Normal
VAS	visual analog scale
WBC	white blood cell

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 mainly covers statistical and analytical plans for the final analysis after database lock. The key analyses which conducted previously might be re-run using the final data.

The key secondary analyses during RW period using the final data will be re-run for PASI 75 responders at week 52. The re-run analyses are including summary and analysis of PASI 50/75/90/100 response and IGA 0 or 1 response, loss of PASI 75/IGA 0 or 1 response, time to relapse, and DLQI. Since loss of PASI 75 during randomized withdrawal period will be re-run, the primary endpoint – loss of PASI 75 up to week 68 will not be performed in the final analysis. In addition, a summary of PASI 50/75/90/100 response and IGA 0 or 1 response till week 156 will also be provided using retreatment patients after relapse.

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

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

All listings will be presented by treatment sequence.

1.1.1 Changes to statistical methods planned in the protocol

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 (either RW or treatment period) rather than relative to the visit's observed value.

A listing of immunogenicity data will be provided.

A definition of "rebound-like events" was introduced to capture rebound events that occur at any point after stopping therapy; whereas, the definition of rebound includes only rebound events that occur within 8 weeks of stopping therapy.

For rebound and relapse no imputed data will be used and analyses will be based on observed data only.

Full analysis set included subjects having at least one post baseline efficacy assessment.

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.

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 will be defined as those subjects where IRT contact is made by the site either prematurely or inappropriately prior to confirmation of the subject’s final randomization eligibility and double-blind study treatment was not administered to the subject.

PASI 75 non- responders being incorrectly randomized as PASI 75 responders will be analyzed as PASI 75 responders in randomized withdrawal period

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatments has been assigned and have at least one post baseline efficacy assessment and on secukinumab at week 52 of core. 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, the actual stratum will be used in analyses. PASI 75 non- responders being incorrectly randomized as PASI 75 responders will be analyzed as PASI 75 responders in randomized withdrawal period.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during RW period for PASI 75 responders and treatment period for partial responders as well as subjects re-treated after relapse. Subjects will be analyzed according to treatment received.

The treatment received will be set to the treatment randomized. But if a subject has received the wrong treatment during the entire study, the treatment received will be set to this wrong treatment. For those subjects who received erroneously the wrong treatment at least once, an additional listing will be prepared displaying adverse events occurred after the treatment errors.

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
Randomization set	NA	Mis-randomized subject
FAS (Full Analysis Set)	1, 3	No post baseline efficacy assessment
Safety	2, 3, 6	Not treated in the extension

1.3 Treatment group definitions

The following treatment labels (Table 1-2, Table 1-3) will be used for re-run tables and final analysis in the order provided below.

Table 1-2 Treatment groups by subjects group for efficacy analysis

Evaluation of	Analysis Period	Treatment group label (order as listed)	Analysis
Subjects who were PASI 75 responders at Week 52	RW	AIN457 150 mg[1] AIN457 300 mg[2] AIN457 150 mg – Placebo[3] AIN457 300 mg – Placebo[4]	PASI 50/75/90/100 response and IGA 0 or 1 response Loss of PASI 75/IGA 0 or 1 response Time to relapse DLQI
Subjects who were re-treated after relapse with AIN457 150 mg or 300 mg	Treatment	AIN457 150 mg Placebo - AIN457 150 mg[5] AIN457 300 mg Placebo - AIN457 300 mg[6]	PASI 50/75/90/100 response and IGA 0 or 1 response
All subjects	On Treatment Period	AIN457 150 mg stay[7] AIN457 300 mg stay[8] All AIN457 150 mg[9] All AIN457 300 mg[10] AIN457 150 mg only[11] AIN457 150 mg - 300 mg[12] AIN457 300 mg only[13]	Final analysis

[1] AIN457 150mg group includes the PASI 75 responders at week 52 who were randomized to AIN150mg at week 52; and the partial responders at week 52 were continued received AIN 150mg from week 52.

[2] AIN457 300mg group includes the PASI 75 responders who were randomized to AIN300mg at week 52; and the partial responders at week 52 were continued received AIN 300mg from week 52.

[3] AIN457 150mg – Placebo group includes the PASI 75 responders who were assigned AIN 457 150mg during core study, and randomized to placebo at week 52.

[4] AIN457 300mg – Placebo group includes the PASI 75 responders who were assigned AIN 457 300mg during core study, and randomized to placebo at week 52.

[5] Placebo – AIN457 150mg group includes the subjects who were randomized to placebo at week 52, and relapsed then treated by AIN457 150mg during RW period.

[6] Placebo – AIN457 300mg group includes the subjects who were randomized to placebo at week 52, and relapsed then treated by AIN457 300mg during RW period.

[7] AIN457 150 mg stay group includes the subjects who were PASI 75 responders at Week 52 and staying strictly in 150mg AIN457 treatment from Week 52. The subjects received placebo at Week 52 and switched to AIN457 150 mg will not be included in this treatment group. Subjects up-titrated from AIN457 150mg to 300mg during open label period will not be included in this group.

[8] AIN457 300 mg stay group includes the subjects who were PASI 75 responders at Week 52 staying strictly in 300mg AIN457 treatment from Week 52. The subjects received placebo at Week 52 and switched to AIN457 300 mg will not be included in this treatment group.

[9] All AIN457 150 mg group includes all the subjects who were assigned to AIN457 150 mg at Week 52, regardless whether they are initial PASI 75 responder or partial responder at Week 52, or who were assigned to placebo at week 52 but relapsed and retreated by AIN457 150 mg during randomized withdrawal period. The subjects who up titrated to 300 mg during the open label period will be included in the efficacy analysis for this treatment group. For the subjects assigned to placebo group at Week 52 and switched to AIN457 150 mg after relapse, the efficacy data after 16 weeks (including 16 weeks) post AIN457 treatment will be included in this group. In addition, the subgroup analysis will be performed for the following two subgroup groups: 1) Subjects who stayed on AIN457 150mg and never were up-titrated; 2) Subjects up-titrated from AIN457 150mg to 300mg during open label period.

[10]All AIN457 300 mg group includes all the subjects who were assigned to AIN457 300 mg at Week 52, regardless whether they are initial PASI 75 responder or partial responder at Week 52, or who were assigned to placebo at week 52 but relapsed and retreated by AIN457 300 mg during randomized withdrawal period. For the subjects assigned to placebo group at Week 52 and switched to AIN457 300 mg after relapse, the efficacy data after 16 weeks post AIN457 treatment will be included in this group. The subjects up titrated during the open label period will not be included in this group.

[11]AIN457 150 mg only group is from ‘ALL AIN457 150 mg’ group and includes the subjects who were PASI 75 responders or partial responder at Week 52 and staying strictly in 150mg AIN457 treatment from Week 52. The subjects received placebo at Week 52 and switched to AIN457 150 mg will not be included in this treatment group. Subjects up-titrated from AIN457 150mg to 300mg during open label period will not be included in this group.

[12] AIN457 150 mg - 300 mg group is from ‘ALL AIN457 150 mg’ group and includes the subjects who started AIN457 150 mg from Week 52 and up-titrated from AIN457 150mg to 300mg during open label period.

[13] AIN457 300 mg only group is from ‘ALL AIN457 300 mg’ group and includes the subjects who were PASI 75 responders or partial responder at Week 52 and staying strictly in 300mg AIN457 treatment from Week 52. The subjects received placebo at Week 52 and switched to AIN457 300 mg will not be included in this treatment group.

Table 1-3 Treatment groups by subjects group for safety analysis

Evaluation of	Analysis Period	Treatment group label (order as listed)	Comment on treatment group definition
Table/Figure	Entire study Period,	Any AIN 457 150 mg[1]	
		Any AIN 457 300 mg[2]	
		Any AIN 457 dose	
		AIN 457 150 mg – Placebo[3]	Same as in Table 1-1
		AIN 457 300 mg – Placebo[4]	Same as in Table 1-1
	Follow-up Period 2	Any AIN 457 150 mg	
		Any AIN 457 300 mg	
		Any AIN 457 dose	

[1] Any AIN457 150 mg group includes all the subjects who have ever received at least one dose of AIN457 150 mg from Week 52 to Week 256 (Week 260 EOT no dose), regardless whether they are initial PASI 75 responder or partial responder at Week 52. For the subjects assigned to placebo group at Week 52 and switched to AIN457 150 mg after relapse or started AIN457 150 mg during open label period, the safety data during and after 1st AIN457 dose will be included in this group. For subjects starting with 150 mg AIN457 dose and switched to 300 mg AIN457, the period used the low dose will be counted for the 'Any AIN457 150mg' group.

[2] Any AIN457 300 mg group includes all the subjects who have ever received at least one dose of AIN457 300 mg from Week 52 to Week256 (Week 260 EOT no dose), regardless whether they are initial PASI 75 responder or partial responder at Week 52. For the subjects assigned to placebo group at Week 52 and switched to AIN457 300 mg after relapse or started AIN457 300 mg during open label period, the safety data during and after 1st AIN457 dose will be included in this group. For subjects starting with 150 mg AIN457 dose and switched to 300 mg AIN457 at any time, the period after switching to the high dose will be included in the 'Any AIN457 300 mg' group.

[3] AIN457 150mg – Placebo group includes the PASI 75 responders who were assigned AIN 457 150mg during core study, and randomized to placebo at week 52. Only data for subjects received placebo period were included in safety analysis.

[4] AIN457 300mg – Placebo group includes the PASI 75 responders who were assigned AIN 457 300mg during core study, and randomized to placebo at week 52. Only data for subjects received placebo period were included in safety analysis.

So, for re-run efficacy analysis the data will be analyzed for RW period. Regarding retreatment patients after relapse, the data till week 156 will be presented. For data analysis till week 156, the following treatment groups will be reported

- **Subjects who were PASI 75 responders at Week 52**

AIN457 150 mg
AIN457 300 mg

AIN457 150mg - Placebo
AIN457300mg - Placebo

- **Subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg**

AIN457 150 mg
AIN457 300 mg
Placebo - AIN457 150 mg
Placebo – AIN457 300 mg

For **final** analysis, the following treatment groups will be reported for the on treatment period.

AIN457 150 mg stay

AIN457 300 mg stay

All AIN457 150 mg

All AIN457 300 mg

AIN457 150 mg only

AIN457 150 mg - 300 mg
AIN457 300 mg only

The following study periods will be considered for analysis:

- **Screening** period (before Randomization in extension)
- **Randomized** withdrawal (RW) period for subjects who were PASI 75 responders at Week 52- the duration of RW period for each subject is different i.e., starting from Week 52 until the subject experiences the first full relapse for efficacy analyses and until the subjects reinitiating the secukinumab after first full relapse for safety analyses. RW period is not fixed for all the subjects but varies for subject to subject based on occurrence of relapse. Subjects not experiencing the relapse will end their RW period at Week 156.
- **Treatment** period for subjects with relapse (for efficacy analyses it is starting from the visit in RW period at which a subject experiences first full relapse to Week 156. Safety analysis will not be re-run for subjects with relapse).
- **Treatment** period for subjects with partial response (Week 52 to Week 156)
- **Open label** period for subjects who were continued in the study and were unblinded at Week 156. The first open label dose were given at the site at Week 156. Subjects previously randomized to receive 150 mg secukinumab may continue with 150 mg secukinumab open label or may switch to 300 mg s.c. at the discretion of the investigator. Subjects previously randomized to 300 mg secukinumab continued with 300 mg secukinumab open label. Placebo subjects who entered the open label period were given once weekly s.c. injections of secukinumab for 4 consecutive weeks and then s.c. injections every 4 weeks. Any subject starting on secukinumab 150 mg may continue on 150 mg every 4 weeks or switch to 300 mg at Week 156 or any other regular site visit if the investigator decided the subject would benefit from the higher dose. The Week 244 visit was the last scheduled visit at which the subjects were allowed to switch to 300 mg dose. Decreasing the dose from 300 mg to 150 mg was not allowed.
- **Follow-up (FU)** period (for all subjects)*: treatment free period (Week 264 to Week 268).

- **Follow-up 2 （FU 2）** period: treatment free period only for subjects who prematurely discontinued treatment. All subjects who prematurely discontinued treatment should complete all assessment of Week 260 (end of treatment visit) and of the follow-up period visits (Weeks 264 and 268). Subsequently, adverse events and use of concomitant medication were evaluated by the investigator through telephone calls every 3 months for duration of 4 years from the time when subject has been enrolled into CAIN457A2302E1 study.
- **Entire study period** = Combination of RW period + treatment period for subjects with relapse and treatment period for subjects with partial response + open label period (Week 156 – Week 260) + follow-up period (Week 264 – Week 268).
- **On treatment period** = Combination of RW period + treatment period for subjects with relapse and treatment period for subjects with partial response + open label period (Week 156 – Week 260).

The number of subjects in the analysis sets may differ between the study periods listed above.

The primary and secondary efficacy variables for final analysis are described as in table 1-4.

Table 1-4 Analysis by period

Endpoint/analysis	Period					
	RW	treatment (re-treated after relapse)	treatment (partial responders)	On treatment period	Follow-up	Entire study period
Demography & baseline characteristics	X					X
Previous & concomitant medication						X
Medical history						X
Study medication: duration of exposure						X
Loss of PASI 75 response over time after 52 weeks of treatment	X					
PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time	X	X[2]		X		
Loss of IGA 0 or 1 response over time after 52 weeks of treatment	X[1]					

Endpoint/analysis	Period					
	RW	treatment (re-treated after relapse)	treatment (partial responders)	On treatment period	Follow-up	Entire study period
PASI score over time				X		
IGA mod 2011 score over time				X		
Relapse					X	
Rebound					X	
EQ-5D				X		
DLQI	X			X		
HAQ©-DI				X[3]		
DLQI 0 or 1 achievement	X			X		

Note:
X[1]: restricted to the subset of subjects who have been IGA 0 or 1 responder at Week 52
X[2]: for subjects who re-treated with secukinumab
X[3] :for subjects with PSA at baseline of the core study

1.4 Subgroup definitions

No subgroup analyses will be conducted for final analysis.

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

1.5.1 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 extension.

1.5.2 Study Day 1 and other study days

Study day is defined with respect to extension. The first day of administration of randomized study treatment (first dose) in extension 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.

1.5.3 Screening (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 (for safety analysis) or prior to the randomization date in extension (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose in extension. Further information will be found in [RAP Module 8].

Baseline is defined with respect to core and extension as follows:

Core baseline:

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

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

Of note, as core baseline measurements are already identified in the core studies, they can be readily used for the purpose of extension study.

Extension baseline:

For efficacy analyses, extension baseline is the last assessment (including unscheduled visits) obtained on or after Week 52 and before the randomization in extension. All assessments obtained after randomization in extension are considered as post-baseline unless otherwise specified.

For safety analyses, extension baseline is the last assessment (including unscheduled visits) obtained on or after Week 52 and before the first dose of study treatment in extension. All assessments obtained after the first dose of study treatment in extension 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 patient reported outcomes (e.g. patient's assessment of PSA pain), lab, ECG, if no pre-treatment value exists a value recorded after first dose can also be used as baseline if it was collected on the same day as first dose.

For efficacy analyses, core baseline will be used for PASI and IGA related variables, such as PASI response, PASI score, et al. Extension baseline will be used for PRO variables.

For safety analyses, extension baseline will be used for all safety variables if not specified.

1.5.4 Visits windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are 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 1-5. In this table, the days are counted since the first dose of study treatment in extension (study days in extension) for safety assessments and the days are counted since the date of randomization in extension 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 56* 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 60*. 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 in section 1.5.5.

Of note, subjects are allowed to have gaps in visits.

The analysis visit will be used for listing of visit and period. If a visit falls after the last visit window (after Day 1527 in the example below) it is not assigned to analysis visit and will be listed under label “After Week 268”.

For the open label period, only the scheduled site visits are included in the table below.

Table 1-5 Visit windows for scheduled visits relative to Week 52

Analysis Visit	Week (relative to baseline of core)	Scheduled Day	Visit Window
Week 52/baseline	52	1	Up to Day 1*
Week 56	56	29	Day 2-43
Week 60	60	57	Day 44-71
Week 64	64	85	Day 72-99
Week 68	68	113	Day 100-127
Week 72	72	141	Day 128-155
Week 76	76	169	Day 156-183
Week 80	80	197	Day 184-211
Week 84	84	225	Day 212-239
Week 88	88	253	Day 240-267
Week 92	92	281	Day 268-295
Week 96	96	309	Day 296-323
Week 100	100	337	Day 324-351
Week 104	104	365	Day 352-379
Week 108	108	393	Day 380-407
Week 112	112	421	Day 408-435
Week 116	116	449	Day 436-463
Week 120	120	477	Day 464-491
Week 124	124	505	Day 492-519
Week 128	128	533	Day 520-547
Week 132	132	561	Day 548-575
Week 136	136	589	Day 576-603
Week 140	140	617	Day 604-631
Week 144	144	645	Day 632-659
Week 148	148	673	Day 660-687
Week 152	152	701	Day 688-715
Week 156	156	729	Day 716-743
Week 168	168	813	Day 744-855
Week 180	180	897	Day 856-939
Week 192	192	981	Day 940-1023
Week 208	208	1093	Day 1024-1149
Week 220	220	1177	Day 1150-1219
Week 232	232	1261	Day 1220-1303
Week 244	244	1345	Day 1304-1387
Week 260	260	1457	Day 1388-1471
Week 264	264	1485	Day 1472-1499
Week 268	268	1513	Day 1500-1527
8 WK after last study drug admin.**			Week 264 visit

12 WK after last study drug admin.**			Week 268 visit

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

** 8/12 WK after last study drug administration will be used for re-bound analysis.

For parameters which are not collected at every visit (e.g. DLQI, EQ-5D, HAQ-DI), visit windows defined in Table 1-5 will be combined. For example, if a parameter is measured at Week 64 and Week 76 only, Week 64 visit window will extend from Day 2 to Day 99 (combining Week 56 to Week 64 visit windows), Week 76 will extend from Day 100 to Day 183 (combining Week 68 to Week 76). If more than one assessment falls into the interval, the rules defined in section 1.5.5 below are applied.

Assessments from treatment period will not be considered for RW period. Assessments from RW period will not be considered for treatment period. Assessments from RW and treatment period may be considered for follow-up period.

Assessments from RW/treatment period will not be considered for open label period. Assessments from open label period will not be considered for RW/treatment period.

The 'by visit' safety summaries for the 'whole treatment period' will be reported as per the analysis visits relative to Week 52 as defined in Table 1-5.

Of note, for subjects who discontinue in RW period, i.e. not moving into treatment period, efficacy measurements taken in follow-up period would still be considered for RW period as specified in Section 1.9.4.1.

1.5.4.1 Visits windows for subjects with relapse

Visit windows for subjects who relapsed (either in PASI 75 responders or partial responders) will be defined analogously to general visit windows as defined in section 1.5.4, but the days are counted since the date of relapse for efficacy assessments including PASI response and IGA 0/1 response. The visit windows are shown in Table 1-6.

Table 1-6 Visit windows for subjects re-treated after relapse

Analysis Visit	Week after relapse	Day	Visit Window
Week 0	0	1	Up to Day1
Week 1 after relapse[1]	1	8	day 2-11
Week 2 after relapse[1]	2	15	day 12-18
Week 3 after relapse[1]	3	22	day 19-25
Week 4 after relapse	4	29	day 26-43
Week 8 after relapse	8	57	day 44-71
Week 12 after relapse	12	85	day 72-99
Week 16 after relapse	16	113	day 100-127
Week 20 after relapse	20	141	day 128-155
Week 24 after relapse	24	169	day 156-183
Week 28 after relapse	28	197	day 184-211
Week 32 after relapse	32	225	day 212-239
Week 36 after relapse	36	253	day 240-267
Week 40 after relapse	40	281	day 268-295
Week 44 after relapse	44	309	day 296-323
Week 48 after relapse	48	337	day 324-351
Week 52 after relapse	52	365	day 352-379
Week 56 after relapse	56	393	day 380-407
Week 60 after relapse	60	421	day 408-435
Week 64 after relapse	64	449	day 436-463
Week 68 after relapse	68	477	day 464-491
Week 72 after relapse	72	505	day 492-519
Week 76 after relapse	76	533	day 520-547
Week 80 after relapse	80	561	day 548-575
Week 84 after relapse	84	589	day 576-603
Week 88 after relapse	88	617	day 604-631
Week 92 after relapse	92	645	day 632-659
Week 96 after relapse	96	673	day 660-687
Week 100 after relapse	100	701	day 688-715
Week 104 after relapse	104	729	day 716-743
Week 108 after relapse	108	757	day 744-771

[1] = Applicable for subjects with relapse in RW period only.

1.5.5 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 1-5 & Table 1-6).

For subjects with relapse switching from PBO to AIN XX, the assessments taken while subject receiving placebo will be considered in RW period and the assessments taken while secukinumab will be considered in treatment period.

For baseline assessment definition see Section 1.5.3. 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 1-7 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 1.5.3
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.

Timing of measurement	Type of data	Rule
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 earlier one will be used. If two measurements are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first visit number (assuming this is the planned visit).
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).

1.5.6 Day of last dose of randomized study treatment

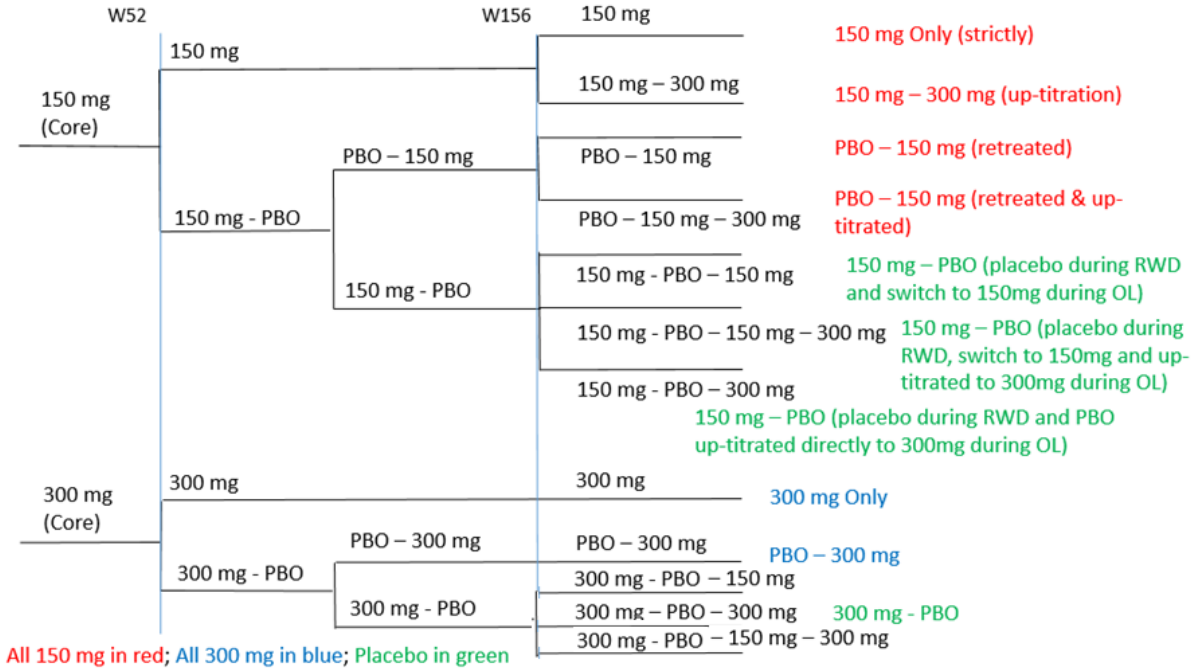
The date of last dose will be collected in the CRF. The subject's exposure will not be calculated using last dose. It will be calculated considering the last visit in RW period for PASI 75 responders and last visit in treatment period for partial responders as well as subjects re-treated after relapse. If a subject in RW period discontinued early, then the last visit during the RW period is considered. If a subject in treatment period discontinued early, then the last visit during the treatment period is considered.

1.6 Subject disposition, background and demographic characteristics

1.6.1 Subject disposition

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 study period for each treatment group and all subjects.

Since the study design is very complicated, the disposition will be provided based on below flow chart.



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

1.6.2 Background and demographic characteristics

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

Continuous variables:

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

Categorical variables:

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

Psoriasis specific baseline characteristics and history of disease will be summarized as well: baseline PASI(at core study baseline and extension baseline), extension baseline PASI 75 responders, extension baseline PASI partial responders, baseline IGA mod 2011 score (at least mild, moderate, severe) (at core study baseline and extension baseline), types of previous psoriasis therapies at core study baseline , 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.

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 at core study baseline and extension baseline. If there is no weight recorded prior to taking of study treatment, 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 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.

1.6.3 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. Concurrent or medical history of disease of interest will be summarized by categories and treatment group.

All the medical history information will be retrieved from the core studies.

1.7 Study medication

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

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. This applies for example 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 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 in the extension will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain time thresholds will be displayed. The following categories will be presented: “any exposure”, “≥4 weeks”, “≥8 weeks”, “≥12 weeks”, and so on with an increase of time threshold by 4 weeks until there are some subjects in the category or the last category “≥256 weeks” is presented.

Duration of exposure will be defined and summarized as follows:

Duration of exposure is defined as the time from first dose of study medication in the extension to 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 84 days, the end of study treatment exposure will be the date of the last study visit.

Duration of exposure (days) = min ('last study visit' date, last dose date +84) – 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 entire study treatment period.

1.8 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.

Background therapies such as MTX or other DMARDs might be excluded from concomitant medications, if appropriate for the indication.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment in core studies. Any medication given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a **concomitant** medication, including those which were started pre-baseline and continued into the RW period/ treatment period.

Indication specific summaries of prior and/or concomitant medication might be presented as well.

For psoriasis this will be done for:

- the categories presented in Table 1-8, but as well for topical, phototherapy and photochemotherapy (yes/no)
- ongoing use of emollients

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

Prior medications will not be re-summarized for extension. They have been summarized in core studies.

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.

Table 1-8 Subgroups based on the previous psoriasis therapy

Level 1 description	Level 1 outcome	Level 2 description	Level 2 outcome	Level 3 description	Level 3 outcome	Level 4 description	Level 4 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	failure*	no		
					yes		
		anti-TNF	No				
			Yes	failure*	no		
					yes	lack of primary efficacy	no
							yes
						lack of secondary efficacy	no
							yes
						lack of primary or secondary efficacy	no
							yes
						lack of tolerability	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

1.9 Efficacy evaluation

1.9.1 Variables

Table 1-9 lists the all primary, secondary and exploratory variables for this study. Only part of the variables will be included in the final analysis. The key secondary variables will be re-run for patients who randomized to RW period or for retreated patents after relapse.

Table 1-9 Primary, secondary and exploratory variables

Variable	Type	Analysis
cumulative rate of subjects who lost PASI 75 response up to Week 68 (compared to placebo) after 52 weeks of treatment	Primary	No analysis
PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time	Secondary	Final analysis Re-run during RW period and for relapse patients after re-treated
Loss of PASI 75 response over time after 52 weeks of treatment	Secondary	Re-run during RW period
Loss of IGA 0 or 1 response over time after 52 weeks of treatment	Secondary	Re-run for PASI 75 responders during RW period
PASI score over time	Secondary	Final analysis
IGA mod 2011 score over time	Secondary	Final analysis
Relapse	Secondary	Final analysis
Rebound	Secondary	Final analysis
Time to PASI 75 response	Secondary	No analysis
Time to IGA 0 or 1 response	Secondary	No analysis
EQ-5D	Secondary	Final analysis
DLQI	Secondary	Final analysis Re-run during RW period
DLQI 0 or 1 achievement	Secondary	Final analysis Re-run during RW period
HAQ-DI score over time[1]	Exploratory	Final analysis
HAQ-DI response over time[1]	Exploratory	Final analysis
[redacted]		

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

1.9.1.1 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 1-12.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) was derived as indicated in Table 1-12. 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 1-10).

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).

It should be noted that the true area percentage values were rounded in the eCRF calculations up to the closest integer value. For example, the true area of 0.45% was rounded to 0% (giving area score of 0), and the true area of 0.5% was rounded to 1% (giving area score of 1).

In order to investigate the effect of rounding the true area percentage values on the PASI scores, an additional calculation of PASI scores without rounding the true area percentage values will be done. The area affected by psoriasis within each anatomic area is estimated as a percentage and assigned a numeric value (area score) according to degree of involvement as follows: no involvement = 0; >0% to <10% = 1; 10% to <30% = 2; 30% to <50% = 3; 50% to <70% = 4; 70% to <90% = 5; and 90% to 100% = 6. The PASI score will be calculated using the formula above. The PASI score calculated in this way will be referred to as the PASI score without rounding the true area percentage values.

Table 1-2 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 = 0% 1 = 1-9% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 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 non response:** subjects achieving <50% improvement (reduction) in PASI score compared to baseline are defined as PASI non responders
- **Partial response**: subjects achieving ≥ 50% improvement (reduction) in PASI score but less than 75% compared to baseline are defined as partial responders
- **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)
- **Relapse**: when the achieved maximal PASI improvement from baseline PASI in core is reduced by >50%
- **Rebound-like event**: defined as increase of PASI of more than 25% from baseline value or occurrence of new pustular, new erythrodermic or more inflammatory psoriasis **after** stopping therapy
- **Rebound**: defined as rebound like event occurring **within 8 weeks** of stopping therapy

The analysis of rebound will be done for the follow-up period.

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

- For rebound, all assessments done up to 8 weeks will be summarized.
- Similarly for rebound like events, all assessments done up to 12weeks will be summarized.
    1. Rebound up to 8 weeks: For this time-point the worst outcome (i.e. rebound like event=yes) prior to this cut-off is considered (e.g. if a subject had >25% PASI increase at Week 260, but not at Week 264 the subject would be considered as rebounder for this “up to 8 week timepoint”).
- Rebound like events up to 12 weeks: For this time-point the worst outcome (i.e. rebound like event=yes) prior to this cut-off is considered.

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 1-11) 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 1-3 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.

1.9.1.2 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 1-12. 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 1-4 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)

1.9.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 1-13.

Table 1-5 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Cochran-Mantel-Haenszel test	Logistic regression	Summary statistics for continuous data	Time-to-event data analysis	Graphs
PASI 50/75/90/100 over time	X	X	X			X[1]
Loss of PASI 75 response over time during RW period	X				X	
Loss of IGA 0 or 1 response over time during RW period	X				X	
Absolute PASI score over time				X		
% change PASI over time				X		
IGA mod 2011 0 or 1 response over time	X	X	X			
IGA mod 2011 score over time by categories				X		
Relapse	X				X	X
Rebound	X					
EQ-5D	X			X		
Absolute DLQI[4]				X		
% change DLQI[4]				X		
DLQI 0 or 1 achievement	X					
HAQ-DI score over time				X[3]		
HAQ-DI response over time	X[3]					

[1]only for subjects who were PASI 75 responders at Week 52
[3]only for subjects with psoriatic arthritis at baseline
[4]additional analyses for subjects who were PASI 75 responders at Week 52 described below

1.9.2 Statistical hypothesis, model, and method of analysis

The statistical hypotheses are that the cumulative rate for subjects who lost PASI 75 response up to Week 68 are not different between secukinumab 150 mg and corresponding placebo as well as between secukinumab 300 mg and corresponding placebo.

Loss of PASI 75 response will be analyzed by means of a survival analysis defining “loss of PASI 75 response” as “failure”. The term *cumulative rate* corresponds to 1 minus the survival function within this survival analysis, and the cumulative rate as well as the survival functions are dependent on time *t*.

Hence, the null hypothesis for each dose corresponds to the usual null hypothesis within a survival analysis: The survival functions of the two groups are not different and will be tested versus the alternative, that the survival functions are different.
If the survival functions are different, they must be different at at least one time point within the analysis period. The analysis period in the primary analysis is Week 52 to Week 68.

Let pj(*t*) denote the proportion of PASI 75 responders at time *t* for treatment group *j,* and let p0,j*(t)* denote the proportion of PASI 75 responders at time *t* for placebo group *j*, *j*=1, 2, where

- 0,j corresponds to placebo (secukinumab 150 mg in core studies) for j=1 and to placebo (secukinumab 300 mg in core studies) for j=2,
- 1 corresponds to secukinumab 150 mg,
- 2 corresponds to secukinumab 300 mg.

The following hypotheses will be tested for 52 weeks≤ t ≤68 weeks

- H_1: $p_1(t) - p_{0,1}(t) = 0$ for all *t*, 52 weeks≤ *t* ≤68 weeks, versus H_{A1}: there is at least one *t* with $p_1(t) - p_{0,1}(t) \geq 0$,
- H_2: $p_2(t) - p_{0,2}(t) = 0$ for all *t*, 52 weeks≤ *t* ≤68 weeks, versus H_{A2}: there is at least one *t* with $p_2(t) - p_{0,2}(t) \geq 0$,

In other words

- H1: Secukinumab 150 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68
- H2: Secukinumab 300 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68

The primary analysis will not be conducted in the final analysis, instead loss of PASI 75 response during RW will be tested.

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

For loss of PASI 75 response, between-treatment differences will be evaluated using a log-rank test, stratified by geographical region and body weight stratum, to compare the survival functions between secukinumab treatment groups versus placebo. The hazard ratios for these comparisons for loss of PASI 75 response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group, core study and baseline PASI of core study and baseline PASI of extension study as explanatory variable and stratified by geographical region and body weight stratum.

Kaplan-Meier estimates including 95% confidence intervals for cumulative rate of subjects losing PASI 75 response will be calculated for each treatment group.

The number of subjects with loss of PASI 75 response, number of subjects in the analysis set, estimate of cumulative rate during RW period, median event time, and its estimated standard

error, as estimable will be provided for each treatment group. In addition, for pre-specified time intervals (e.g., 4-week intervals) the following will be presented:

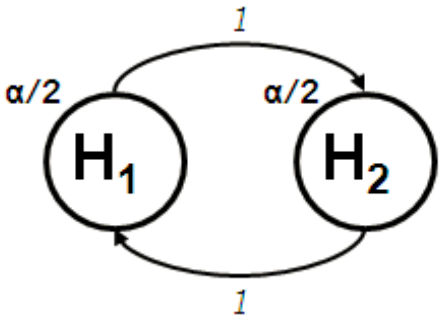
- for each treatment group and time interval: subjects at risk, subjects with loss of PASI 75 response, subjects with loss of PASI 75 response divided by subjects at risk, cumulative subjects with event and cumulative event probability including 95% confidence interval.
- for treatment comparisons the log-rank test and Wilcoxon test as well as the hazard ratio derived via Cox regression.

1.9.3 Testing strategy

The family wise error will be set to α=2.5% (one-sided). The two hypotheses H1 (referring to 150 mg) and H2 (referring to 300 mg) will be tested at α/2=1.25% one-sided. In case, a null hypothesis has been rejected for one dose, but not for the other dose, the alpha can be shifted to the other dose and the null hypotheses can be retested at level α=2.5% (one-sided).

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

Figure 1-1 Testing strategy



Note - Other secondary endpoints will not be included in the testing strategy.

1.9.4 Handling of missing values/censoring/discontinuations

For the analyses re-run during RW period

The loss of PASI 75 response during RW period will be re-run. The subjects who have no lost PASI 75 response during RW will be considered as censored observations. Subjects who have not lost PASI 75 response but with missing values during RW will be considered as censored at prior available visit. Subjects who administered psoriasis concomitant medication (as per [MAP Appendix]), will be considered as failures at time of first administration if this occurred before the loss of PASI 75. Subjects who did not have PASI 75 response but randomized in RW period will be censored at day 0. Subjects with missing values at week X (X <156) and who have not lost PASI 75 response earlier, will be censored at week X (if they have not dropped out due to lack of efficacy or not administered psoriasis concomitant medication). Subjects who drop-out due to lack of efficacy will be considered as failure at time of drop-out. If drop-out was due to other reason, subjects will be considered as censored at time of drop-out. Intermediate missing values will not be considered.

Other time-to-event analyses will be handled analogously. For imputation techniques, please refer to Table 1-16.

For other analyses (not time to event) missing values with respect to response variables based on PASI score and IGA mod 2011 score will be imputed with multiple imputation regardless of the reason for missing data (e.g., premature study discontinuation, missed visit, administrative issues).

Following the intent-to-treat principle for subjects who prematurely discontinue treatment, but who are observed in the follow-up period, efficacy data collected in follow-up periods will be linked to planned but missed study visits as well, following imputation schemes described in Sections 1.5.4.1 and 1.9.4.2. (e.g., if a subject discontinues treatment at Week 56, but has follow-up visit F4, the PASI score observed at Visit F4 might be used for Week 60 assessments).

For rebound and relapse no imputed data will be used and analyses will be based on observed data only.

The last observation carried forward method (LOCF) will be applied to PASI score and IGA mod 2011 score that are missing after baseline regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Note that LOCF imputations will not be considered for response variables based on PASI score or IGA score which will be imputed with non-response, see above. Baseline values will not be carried forward.

If all post Randomization Visit efficacy values are missing for one efficacy parameter then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable, *i.e.*, it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS. In addition, missing baseline values will not be imputed.

For subjects who were re-treated after relapse with secukinumab 150 mg or secukinumab 300 mg amongst PASI 75 responders at week 52, values of RW period are not carried forward to treatment period.

For HAQ score and derived variables, EQ-5D and DLQI missing values will be replaced by LOCF. Missing responses will also be imputed by LOCF. Baseline values will not be carried forward.

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 ">")."

For the final analysis

For subjects who prematurely discontinue treatment, but are observed in the follow-up period, efficacy data collected in follow-up periods will not be linked to planned study visits.

The following missing data imputation methods will apply to PASI and IGA score or response variables in the final analysis:

- Response variables based on PASI score and IGA mod 2011 categories will be generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.
- For subjects who received secukinumab dose from week 52, multiple imputation will be used as the sensitivity method

1.9.4.1 Details for imputations (non- responder and LOCF) and visit windowing

Note: These details are not applicable to time to event analysis. Only PASI and IGA mod 2011 based response variables are imputed with non-response, other response variables (e.g. for HAQ-DI, EQ-5D, DLQI) will be imputed with LOCF. Baseline values will not be carried forward. If all post baseline values are missing for one efficacy parameter, then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable.

- Non- responder imputation for subjects with PASI 75 response at Week 52 - RW period (Week 52 up to Week 156)
  1. Assign period to each visit as per CRF visit (CRF period) or as per visit date for unscheduled visits (analysis period)
  2. Assign analysis visit windows (for RW period from week 52 up to Week 156) according to Section 1.5.4. Of note, RW CRF period visits will not be assigned to treatment analysis period, whereas follow-up period CRF visits might be assigned to RW analysis period for subjects who do not enter treatment CRF period)
  3. If no CRF visit is assigned to an analysis visit as per Section 1.5.4, impute non-response

Note – Subjects with PASI 75 response at week 52 enter RW period. RW period is not fixed for all the subjects but varies for subject to subject based on occurrence of relapse. Subjects in RW period will enter treatment period only after first full relapse, if it occurs; otherwise not. Partial responders are not entering the RW period but go into the treatment period.

- LOCF imputation

1. Assign period to each visit as per CRF visit (CRF period) or as per visit date for unscheduled visits (analysis period)
2. Assign analysis visit windows (for RW period from week 52 up to Week 156) according to Section 1.5.4. Of note, RW CRF period visits will not be assigned to treatment analysis period, whereas follow-up CRF period visits might be assigned to RW analysis period for subjects who do not enter treatment CRF period)
3. If no CRF visit is assigned to an analysis visit as per Section 1.5.4, impute with LOCF

Note: All data collected in the eCRF will be considered for LOCF imputation regardless of whether the data was considered in analysis visit windows.

1.9.4.2 Multiple imputations

Loss of PASI 75 response will be evaluated as described above in section 1.9.2 with multiple imputations instead of non-responder imputation for missing values. Multiple imputation will also be used for PASI/IGA score and responses variables.

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' will be imputed 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.

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. Values post assessment timepoint of the primary endpoint will not be considered for imputations.

The number of imputations will be set to 100, the seed for the random function will be set to 457230201 for this study. To generate the multiple imputed data sets, the SAS procedure MI can be used as follows:

The input data set <pasi> should have one record per subject with baseline PASI as well as all changes from baseline PASI score.

```
ODS LISTING CLOSE;

PROC MI DATA=<pasi> OUT=<impdata> SEED=457230201 NIMPUTE=100;
EM maxiter=300;
 VAR <baseline weight>
    <failure to at least one biologic>
    <number of previous systemic therapies>
    <baseline PASI>
    <change from baseline PASI week 52>
    <change from baseline PASI week 56>
    <change from baseline PASI week 60>
    <change from baseline PASI week 64>
    <change from baseline PASI week 68>

  BY <treatment group>;
RUN;
ODS LISTING;
```

The imputed data are saved in data set <impdata>. The outcomes of interest, i.e. the loss of PASI 75 response will be calculated from change from baseline PASI scores. The day of visit at which the first occurrence of losing PASI 75 response will also be obtained. In the case of missing visits or visit dates the planned visit day will be used., 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;
END;
RUN;
```

The treatment differences for each imputed data set will then be evaluated by using Cox proportional hazards regression as described section 1.9.2. This analysis will be done by _IMPUTATION_ for each pairwise comparison as described in section 1.9.5. The data set should be sorted such that the control group comes last. E.g as follows:

```
ods table HazardRatios = hazardratios;
proc phreg data = <impdata2>;
class <treatment group> <core study> <geographical region> <body weight stratum>
 model TIME*PASI75(1)= <treatment group> <core study> <core baseline PASI> <extension baseline PASI>/ties=exact;
STRATA < geographical region> < body weight stratum>
 by _Imputation_;
run;
        data dhazardratios;
                set hazardratios;
                where Description in ( 'TRT01PN 1 vs 3' 'TRT01PN 2 vs 4');
                if Description in ( 'TRT01PN 1 vs 3') then comp =1;
                else if Description in ( 'TRT01PN 2 vs 4') then comp =2;
                if HazardRatio NE . and HazardRatio > 0 then ESTIMATE=log(HazardRatio);
                if WaldLower NE . and HazardRatio > 0 then STDERR=log(WaldLower/HazardRatio)/-probit(1-0.05/2);
                if missing(ESTIMATE) or missing(STDERR) then delete;
        effect="LogHR";
        run;
```

- The PHREG procedure and following MIANALYZE procedure could then be run with by-variables for the comparison and response identifier.

The MIANALYZE procedure expects the parameter estimate in the variables ESTIMATE, and the corresponding standard error in the variable STDERR. The dataset dhazardratios above contained the estimate and its standard error for log(Hazard ratio)

The estimates and standard errors of the log of hazard 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).

The SAS procedure MIANALYZE will be applied as follows:

```
ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=<results>;
PROC MIANALYZE PARMS=<lgparms>;
  BY comp;
   MODELEFFECTS LogHR;
RUN;
ODS LISTING;

DATA <results2>;
  SET <results>;
  or=EXP(estimate);
  lowercl=EXP(LCLmean);
  uppercl=EXP(UCLmean);
  KEEP <By-variables> or lowercl uppercl probt;
RUN;
```

1. **Cumulative Probabilities and CI:** Use log(-log(x))-transformed estimates for the survival function and their associated standard errors for each imputed data set and combine the results using Rubin's rules (PROC MIANALYZE). The transformation is done to ensure that resulting confidence intervals only include values between 0 and 1.
    1. Then back-transform combined estimates and associated CI intervals and calculate the 'cumulative' quantities.
    2. Calculate the mean across all imputed data sets for the columns: "subj. at risk" / "subj. with event" / "subj. with event/at risk"/ "cum. subj. with event", round them to the nearest integers as these will generally be non-integers.

Steps for Cumulative Probabilities and CIs:

1. Create 100 imputed datasets including time to loss of PASI 75 response for each patient using PROC MI.
2. Run PROC LIFETEST for each imputed data set and store estimates for the survivor function (SURVIVAL) and the associated standard errors (STDERR) in the data set OUTSURV.

```
proc lifetest data=adttepas method=km outsurv=outsurv;
        by _imputation_;
        strata arm;
        time aval*cnsr(1);
run;
```

3. In a data step use the data set OUTSURV to calculate
    1. T_SURVIVAL=log(-log(SURVIVAL))
    2. T_STDERR= STDERR/(SURVIVAL*log(SURVIVAL))

```
data outsurv1;
set outsurv;
```

```
            T_SURVIVAL=log(-log(SURVIVAL));
                T_STDERR= STDERR/(SURVIVAL*log(SURVIVAL))
    run;
```

4. Use the data set OUTSURV1 as input for PROC MIANALYZE to combine the results for T_SURVIVAL and T_STDERR based on the multiply imputed data sets. As we have two strata and different time intervals, we combine the estimates separately for each combination =strata * time interval.

```
ods output ParameterEstimates=Survival_MI;
proc mianalyze data=outsurv1;
   by combination;
   modeleffects T_Survival;
   stderr T_STDERR;
  run;
```

5. Back-transform the combined survival estimates to the original scale and calculate the cumulative probabilities and associated CIs

```
data Survival_MI2;
set Survival_MI;
        MI_survival=exp(-exp(Estimate));
            LCL=(MI_survival)^exp(quantile('NORMAL',.975)*STDERR);
            UCL=(MI_survival)^exp(-quantile('NORMAL',.975)*STDERR);
            MI_cumulative= 1-MI_survival;
            LCL_cum=1-UCL;
            UCL_cum=1-LCL;
run;
```

p-values from Log-rank and Wilcoxon tests: Use transformed estimates for the Log-rank and Wilcoxon test statistics and their associated standard errors for each imputed data set using the Wilson-Hilferty transformation (Wilson & Hilferty, 1931; Goria, 1992) and combine the results using Rubin's rules (PROC MIANALYZE).

Steps for p-values from Log-rank and Wilcoxon tests

1. Create 100 imputed datasets including time to loss of PASI 75 response for each patient using PROC MI.
2. Run PROC LIFETEST for each imputed data set and store estimates for the test statistics and the associated standard errors (STDERR) in the data set HOMTESTS.
3. Apply Wilson-Hilferty transformation to the Chi-square statistic and standardize the resulting normal variable as below e.g.;

```
DATA HOMTESTS1;
```

```
  SET HOMTESTS;
  CHI_VALUE_WH=((ChiSq/DF)**(1/3) - (1-2/(9*DF)))/SQRT(2/(9*DF));
  CHI_STERR_WH = 1.0;
RUN;
```

4. Use the data set HOMTESTS1 as input for PROC MIANALYZE to combine the results for CHI_VALUE_WH and CHI_STERR_WH based on the multiply imputed data sets

```
ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=logrank_mi;
PROC MIANALYZE data=logrank;
                by comp;
                modeleffects chi_value_wh;
                stderr chi_sterr_wh;
RUN;
ODS OUTPUT ParameterEstimates=wilcox_mi ;
PROC MIANALYZE data=wilcox;
        by comp;
        modeleffects chi_value_wh;
        stderr chi_sterr_wh;
RUN;
ODS LISTING;
```

1.9.5 Secondary variables

Secondary variables are:

PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

Loss of PASI 75 response over time in subjects who were PASI 75 responders at Week 52

Loss of IGA 0 or 1 response over time in subjects who were PASI 75 responders as well as IGA 0 or 1 responders at Week 52

PASI score over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

IGA mod 2011 score over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

Relapse in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

Rebound in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

EQ-5D in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

DLQI score as well as DLQI 0 or 1 achievement in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.

1.9.6 Methods of analysis

Final analysis

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

Descriptive statistics will be provided until the last visit. Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit starting from Week 52 onwards 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 percent change from core baseline by visit starting from Week 52 onwards and treatment group.

IGA mod 2011 score over time

Summary statistics for the IGA mod 2011 score over time will be presented by visit starting from Week 52 onwards and treatment group in contingency tables.

Relapse

Relapse will be analyzed analogously to loss of PASI 75 response in the follow-up period.

A listing of these subjects will also be provided.

Rebound

The number and percentage of subjects experiencing rebound during follow-up period will be presented by visit and treatment group.

For subjects who were PASI 75 responders and randomized to RW period

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

Descriptive statistics will be provided until the last visit. Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit starting from Week 52 onwards will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe, 1998).

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response at each visit starting from Week 52 onwards during RW period, each secukinumab dose regimen will be compared to placebo (up to last visit with more than 5% of subjects in placebo group) by means of the stratified Cochran-Mantel-Haenszel-test as well as by means of a logistic regression model with treatment group, geographical region, body weight stratum at core, and core baseline PASI as effects.

Loss of PASI 75 response over time

The loss of PASI 75 response during RW period will be repeated. In addition, the secukinumab treatment groups will also be compared, i.e. a Cox proportional hazards regression will be fitted as described above including all four treatment groups. Placebo (secukinumab 150 mg in core studies) and Placebo (secukinumab 300 mg in core studies) will be compared as well as secukinumab 150 mg and secukinumab 300 mg.

Loss of IGA 0 or 1 response over time

Loss of IGA 0 or 1 response over time will be analyzed analogously to the loss of PASI 75 response, but it will be restricted to the subset of subjects who have been IGA 0 or 1 responder at Week 52.

For subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg

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

Descriptive statistics will be provided from relapse until week 156. Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit will be provided similar as for RW period.

1.9.7 Risk set, timing and censoring for time to event analysis

Subjects at risk, timepoint "0" and censoring will be defined as described in Table 1-14 below.

Table 1-64 Time to event: definition of risk set, timing and censoring by variable

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed	Informative censoring
Loss of PASI 75 response	All PASI 75 responders at Week 52 per analysis visit AND entering RW period as per CRF disposition page	Week 52 per analysis visit	Date of 1st visit with OBSERVED loss of PASI 75 response (i.e. no imputation for missing values)	Last available visit up to Week 68 per analysis visit for PEA & End of RW period for secondary analysis	Event (if the subject took psoriasis ConMed, the subject is considered as having lost response)	Study phase discontinuation with reason "lack of efficacy"

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed	Informative censoring
Loss of IGA mod 2011 0 or 1 response	All IGA 0 or 1 responders at Week 52 amongst PASI 75 responders as per analysis visit AND entering RW period as per CRF disposition page	Week 52 per analysis visit	Date of 1st visit with OBSERVED loss of IGA mod 2011 0 or 1 response (i.e. no imputation for missing values)	Last available visit up to Week 68 per analysis visit for PEA & End of RW period	Event (if the subject took psoriasis ConMed, the subject is considered as having lost response)	Study phase discontinuation with reason “lack of efficacy”
Relapse (in follow-up period)	All subjects who were PASI 50 responders (based on OBSERVED data)at least once during the RW or treatment period	Date of last active treatment or last secukinumab placebo administration	Date of 1st visit with OBSERVED relapse (i.e. no imputation for missing values) after time = 0	End of follow-up period as per CRF disposition page	Event (if the subject took psoriasis ConMed, the subject is considered as having experienced relapse)	Study phase discontinuation with reason “lack of efficacy”

ConMed: Concomitant medication

Psoriasis ConMed is defined in MAP appendix

[redacted]

[redacted]

[redacted]

[redacted]

1.9.9 Biomarkers

Not applicable.

1.9.10 Health-related Quality of Life (HRQoL)

EQ-5D

The EQ-5D is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) 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 visit and treatment group. Chi-square tests will be used to compare treatments groups by visit.

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

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.

For each of the seven scores the percentage change from extension baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group.

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

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.

1.10 Standard safety evaluation

All safety analyses will be based on the safety set. In general, summaries will be provided for extension phase i.e after first dose of study medication in extension. In general, extension baseline will be used for all change from baseline analysis.
Safety analysis will be based on treatment groups as defined in Table 1-3.

1.10.1 Adverse events

Adverse events will be summarized for entire study period.

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 1-15.

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

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

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

Table 1-75 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP/RMP risks (special AE interest)	SAEs	AEs-SMQ	AEs by severity	study treatment related AEs, death&other significant AEs	notables (lab/vitals/ ECG)
entire treatment	•crude incidence •exp.time adjusted incidence*	•crude incidence •exp.time adjusted incidence*	•crude incidence •exp.time adjusted incidence*	•crude incidence	•crude incidence	•crude incidence
follow-up 2	•crude incidence	•crude incidence	NA	NA	NA	NA

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

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

AE of special interest:

Table 1-86 Overview of analyses on some safety endpoints

AE of Special 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)	

The crude incidence of treatment emergent adverse events will be summarized. Only primary paths within MedDRA will be considered for adverse event reporting. (see Section 2.6).

AEs will be summarized by presenting, for each treatment group the number and percentage of subjects having at least one AE at each year interval per treatment group, 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 subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Adverse events will also be summarized by SMQ according to MedDRA using a narrow search.

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

The most common adverse events reported (≥ 2% in any group for each preferred term in the table by SOC and PT or ≥ 2% in any group for each SMQ table) will be presented in descending frequency according to its incidence in secukinumab 300 mg starting from the most common event.

Confidence intervals for relative frequencies will be derived as well according to the score method including continuity correction by Newcombe, 1998.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

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.

The follow-up 2 period data are be presented separately in tables and listings. i.e., AE, SAEand concomitant medications.

Algorithms for date imputations will be provided in PDS.

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

1.10.2 Laboratory data

Laboratory evaluations will be summarized for entire study period.

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology and clinical chemistry). 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 extension to each study visit will be presented by laboratory test and treatment group. Change from extension baseline will only be summarized for subjects with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

Only "on-treatment" laboratory data will be summarized (i.e. assessments within last dose plus 84 days). All laboratory data will be listed with "on-treatment" flag displayed. Follow-up visits (CRF visits) may be summarized separately if required.

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 ">")."

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. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test 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 1-17: hemoglobin, platelets, white blood cell count, platelets, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glucose, cholesterol, triglycerides (TG), amylase and lipase.

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

Table 1-9 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 - 80g/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	>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
Amylase increased	>UNL-1.5 ULN	>1.5 UNL-2.0 ULN	>2 UNL-5.0 ULN	>5.0 ULN
Lipase increased	>UNL-1.5 ULN	>1.5 UNL-2.0 ULN	>2 UNL-5.0 ULN	>5.0 ULN

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

Shift tables will be presented comparing extension baseline laboratory result (CTCAE grade) with the worst post baseline results (expressed in CTCAE grade) during entire study period. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

The number and percentage of subjects with CTCAE grade newly occurring or worsening after extension baseline (treatment emergent) will be presented for entire study 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. Exposure adjusted incidence rate will be presented for nesting groups: CTC grade >=1, CTC grade >=2, CTC grade >=3, CTC grade 4.

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 1-18.

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

Table 1-18 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	>1.5xULN; >2xULN; >3xULN,
ALP	>2xULN; >3xULN; >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & 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 **(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.
Amylase	Amylase >ULN
Lipase	Lipase>ULN
Amylase or Lipase	Amylase or Lipase>ULN
Amylase &Lipase	Amylase and Lipase>ULN
Amylase	Amylase >3xULN
Lipase	Lipase>3xULN
Amylase or Lipase	Amylase or Lipase>3xULN
Amylase &Lipase	Amylase and Lipase>3xULN
Amylase or Lipase & concomitant epig astric pain	Amylase or Lipase>3xULN and concomitant epigastric pain Note: For Concomitant epigastric pain, SOC Gastrointestinal disorders and PT Abdominal pain upper will be used
Amylase & Lipase & concomitant epig astric pain	Amylase and Lipase>3xULN and concomitant epigastric pain Note: For Concomitant epigastric pain, SOC Gastrointestinal disorders and PT Abdominal pain upper will be used

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

1.10.3 Vital signs

Vital signs will be summarized for entire study period.

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

change from baseline = post-baseline value – baseline value

Only "on-treatment" vital signs will be summarized (i.e. assessments within last dose plus 84 days). All vital signs will be listed with "on-treatment" flag displayed. Follow-up visits (CRF visits) may be summarized separately if required.

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 1-19 below.

Listings will be provided on combined data of PASI 75 responders and partial responders.

Table 1-19 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

1.10.4 Electrocardiogram (ECG)

ECG evaluations will be summarized for entire study period.

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 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.

Only "on-treatment" ECG evaluations will be summarized (i.e. assessments within last dose plus 84 days). All ECG evaluations will be listed with "on-treatment" flag displayed. Follow-up visits (CRF visits) may be summarized separately if required.

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

1.10.5 Immunogenicity

A listing of immunogenicity data will be provided.

1.11 Sample size calculation

Assumptions for the number of subjects eligible for RW (i.e for the analysis of primary endpoint):

- Drop-out rate on secukinumab at Week 12 in core studies: 5% (estimate from CAIN457A2211)
- Drop-out rate on placebo at Week 12 in core studies: 15% (from CAIN457A2211)
- Placebo PASI 75 response rate at Week 12: 5% (conservative assumption)
- Drop-out rate on secukinumab up to Week 52 in core studies: 15% (common for secukinumab induction and placebo induction regimens, as in Leonardi et al, 2008)
- PASI 75 response rate at Week 52 on secukinumab 150 mg in core studies: 65% (from dosing rationale in protocols of core studies) (power would be larger for 300 mg if we would assume similar loss of PASI75 rates)
- Type-I-error rate is defined to one-sided 2.5%

With these assumptions it is estimated to have 414 subjects eligible per dose to enter the RW, with a randomization ratio of 2:1 this would be 276 subjects on 150 mg and 138 subjects on placebo. With about 400 subjects the study would have more than
90% power to detect differences in the cumulative rates if 10% of subjects on secukinumab lost PASI 75 response versus 23% on placebo, PASS 2008 software (Log Rank Survival Power Analysis - Simple). [redacted]

2 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

Not Applicable

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