NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457A3302 / NCT02409667

OPTIMISE (OPtimization of Treatment In MaIntenance with SEcukinumab 300 mg)

[Long term clear skin maintenance treatment optimization in patients with moderate to severe chronic plaque psoriasis: A randomized, multicenter, open-label with blinded-assessment, comparative, 52 week study to evaluate the efficacy, safety and tolerability of secukinumab 300 mg s.c.]

RAP Module 3 – Detailed Statistical Methodology for the final analysis

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Document History – Changes compared to previous version of RAP module 3.

Version 0.2

- Removal of specific criteria for inclusion in Per-Protocol Set
- Inclusion of new subgroup categories and respective analyses
- Specification of End of Treatment visits
- Modification of EQ-5D analysis: analysis of single dimensions and usage of EQ-5D utility index based on both, GER and UK values
- Analysis of TB status at Baseline
- Inclusion of PK analysis

Version 1.0

- No further, contentual changes

Version 1.1

- Inclusion of PP-FUS analysis set for the analysis of rebound and relapse
- Removal of indirect response model for PK analysis
- Removal of confidence intervals for risk differences of PASI responder rates
- Inclusion of analysis of AEs of special interest

Version 2.0

- Specification of search strategies for AEs of special interest
- Adaption of age groups for baseline description
- Correction of typos

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List of abbreviations

AE	Adverse event
AESI	AE of special interest
AIN457	Secukinumab
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
BSA	Body Surface Area
BSL	Baseline
CI	Confidence interval
CSR	Clinical study report
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic case report/record form
EQ-5D	EuroQOL 5 Dimension Health Questionnaire
FAS-P75R	Full analysis set for Treatment Period 2 of PASI 75 Responders who do not achieve a PASI 90 Response
FAS-P90R	Full analysis set for Treatment Period 2 of PASI 90 Responders
FU	Follow-Up
HGB	Hemoglobin
HR	Heart rate
HRQoL	Health-related quality of life
IGA	Investigator's global assessment
IGA mod 2011	Novartis investigator's global assessment modified 2011
ITT	Intention-to-treat
LLN	Lower limit of normal
LSM	Least-square means
MACE	Major adverse cardiovascular events

MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
MI	Multiple imputation
NMQ	Novartis MedDRA Query
NovDTD	Novartis Drug and Therapy Dictionary
NRS	Numeric rating scale
PASI	Psoriasis Area and Severity Index
PD	Protocol deviation
PK	Pharmacokinetic
PP-P90R	Per-Protocol Set for Treatment Period 2 of PASI 90 Responders
PRO	Patient Reported Outcome
PT	Preferred term
QT	QT interval for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAF-TP1	Safety set for Treatment Period 1
SAF-TP2	Safety set for Treatment Period 2
s.c.	Subcutaneous(ly)
SOC	System Organ Class
TB	Tuberculosis
TBL	Total bilirubin
TP1	Treatment Period 1
TP2	Treatment Period 2
ULN	Upper limit of normal
VAS	Visual analog scale
WPAI-PSO	Work Productivity and Activity Impairment Questionnaire-Psoriasis

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

Data will be analyzed according to the Section 9 (Data Analysis) of the study protocol (version v01, dated 16 June 2015) which is available in the Appendix of the clinical study report (CSR). Important information is given in the following sections and details are provided, as applicable, in the Appendix of the CSR.

1.1 Statistical and analytical plans

This document covers statistical and analytical plans for the analysis of the study CAIN457A3302. This analysis will be performed after all subjects have completed their final visit, i.e. the Week 60 visit for patients entering the Follow-Up period or the Week 52 visit for all other patients, respectively.

The primary objective is to demonstrate in the patient pool of Psoriasis Area and Severity Index (PASI) 90 responders at Week 24 that secukinumab 300 mg subcutaneous (s.c.) every 6 weeks treatment is non-inferior to secukinumab 300 mg s.c. every 4 weeks treatment with respect to maintaining a PASI 90 response rate at Week 52.

The key secondary objective is to demonstrate in the patient pool of PASI 75 responders who do not reach a PASI 90 response at Week 24 that secukinumab 300 mg s.c. administered every 2 weeks is superior to secukinumab 300 mg s.c. administered every 4 weeks at Week 52 based on the PASI 90 response rate.

Other secondary objectives are:

- To evaluate the proportion of PASI 50, PASI 75, PASI 100 and IGA mod 2011 0/1 responder rates at Week 52.
- To evaluate the course of mean PASI over time from Week 24 to Week 52.
- To evaluate the effect of different maintenance treatment frequencies on PROs: Dermatology Life Quality Index (DLQI), EuroQOL 5-Dimension Health Questionnaire (EQ-5D©), Work Productivity and Activity Impairment Questionnaire-Psoriasis (WPAI-PSO), and the patient's assessment of pain, itching and scaling.

Exploratory objectives are:

- To evaluate the proportion of PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responders at Week 24.
- To evaluate the time to achieve clear or almost clear skin based on PASI 90 when receiving secukinumab 300 mg s.c. every 2 weeks compared to every 4 weeks from Week 24 to Week 52.
- To evaluate time to first loss of PASI 75 response when receiving secukinumab every 2 weeks compared to every 4 weeks from Week 24 until Week 52.
- To evaluate the safety and tolerability of different maintenance treatment regimens of secukinumab 300 mg s.c.

- To explore the correlation between the pharmacokinetic (PK) data and efficacy outcomes.

Other exploratory objectives for patients with PASI 90 response at Week 24 are as follows:

- To assess the time to loss of PASI 90 response.
- To assess the time to loss of IGA mod 2011 0/1 response.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, median, 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%.

Listings will be presented by treatment sequence, if applicable.

1.1.1 Changes to statistical methods planned in the protocol

- Inclusion of Body Weight at Week 24 as exploratory variable in the key secondary logistic regression model
- No calculation of indirect response models for PK data and efficacy as planned in the protocol. Figures will be provided instead.

1.1.2 Footnotes

Footnotes on outputs will be kept to a minimum also for outputs not covered in Efficacy MAP M7.1 Amendment 5 or Safety MAP M7.1 Amendment 4.

Footnotes will generally be provided for

- abbreviations used in the output; abbreviations used on several outputs, e.g. for listings in the Appendix 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 Report 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 in a footnote)
- information that will be provided in the clinical study protocol and/or methods section of the Report (e.g. baseline definition if this is specified in the Report).

1.2 Subjects and treatments

The following study periods will be considered for the analysis:

- **Screening Period** (Screening to Visit 2 [=Baseline], excluding Visit 2 [=Baseline])
- **Treatment Period 1** (Visit 2 [=Baseline] to Week 24 pre-dose)
- **Treatment Period 2** (Week 24 post-dose to Week 52)
- **Follow-Up Period** (Week 52 to Week 60, excluding Week 52).

For Treatment Period 1 (Baseline to Week 24) all patients will receive the same treatment:

- Secukinumab 300 mg s.c. will be self-administered at Baseline, weekly at Week 1, Week 2 and Week 3 and every 4 weeks thereafter (i.e., Week 4, 8, 12, 16 and 20).

At Week 24, all patients will be assessed in term of PASI response and either randomized to one of the 4 treatment groups in Treatment Period 2 (Week 24 to Week 52) or withdrawn from the study. Randomization is stratified by body weight at this visit ("body weight $\geq$ 90 kg" vs. "body weight < 90 kg" at Week 24) in order to ensure balanced allocation of patients to treatment groups within the weight strata.

Patients with at least a 90% reduction in PASI score from Baseline will be randomized at Week 24 on a 1:1 basis to Group 1 or Group 2:

- **Group 1** (recommended maintenance treatment): secukinumab 300 mg s.c. every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- **Group 2** (experimental dosing maintenance treatment): secukinumab 300 mg s.c. every 6 weeks (Week 24, 30, 36, 42 and 48).

Patients with less than 90% reduction in PASI score from Baseline at Week 24 but who achieved at least a 75% reduction in PASI score from Baseline are eligible for dose frequency intensification and will be randomized on a 1:1 basis to either Group 3 or Group 4:

- **Group 3** (recommended maintenance treatment): secukinumab s.c. 300 mg every 4 weeks (Week 24, 28, 32, 36, 40, 44 and 48).
- **Group 4** (experimental maintenance treatment): secukinumab s.c. 300 mg every 2 weeks (Week 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46 and 48).

Patients with a reduction in PASI score from Baseline of less than 75% at Week 24 are not eligible for randomization and are discontinued from the study.

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

Safety set for Treatment Period 1 (SAF-TP1): The safety set for Treatment Period 1 includes all subjects who took at least one dose of study treatment during this treatment period.

Safety set for Maintenance Treatment Period 2 (SAF-TP2): The SAF-TP2 includes all patients who were randomized and received at least one dose of study drug at or after the Week 24 visit. Subjects will be analyzed according to treatment received.

Full analysis set for Treatment Period 2 of PASI 90 Responders (FAS-P90R): The FAS-P90R will include all patients who were rated as PASI 90 responders at the Week 24 visit, randomized to treatment groups 1 or 2 and received at least one dose of study drug at or after visit Week 24.

Full analysis set for Treatment Period 2 of PASI 75 Responders who do not achieve a PASI 90 Response (FAS-P75R): The FAS-P75R will include all patients who were rated as PASI 75 responders but do not achieve a PASI 90 response at the Week 24 visit, were randomized to treatment groups 3 or 4 and who received at least one dose of study drug at or after visit Week 24.

Per-Protocol Set for Treatment Period 2 of PASI 90 Responders (PP-P90R): The PP-P90R will include all patients from the FAS-P90R who complete the study as scheduled without any major deviations from the protocol which may affect the primary outcome of this study. Major deviations will be based on selected protocol deviations as defined in the Data Review Plan and additional criteria which might have impact on the treatment's efficacy. The final classifications of deviations as major (i.e. leading to withdrawal from the PP-P90R) will be performed in a data review before start of the analysis.

Follow-Up set (FUS): all patients from dosing group 3 or 4 who entered the Follow-Up (FU) Period of the study, i.e. who continue into the next phase of the trial at Week 52 and for whom any efficacy or safety data from the FU Period are available.

Per-Protocol Follow-Up set (PP-FUS): all patients from the FUS without any major deviations from the protocol in the follow-up period which may affect the rebound assessment at the end of this period. The final classifications of deviations as major (i.e. leading to withdrawal from the PP-FUS) will be performed in a data review before start of the analysis.

1.3 Subgroup definitions

The primary endpoint, selected secondary endpoints and selected safety endpoints will be evaluated using the subgroups defined in

Table 1-1. Subgroup analyses for the study endpoints are represented in Table 1-2.

Table 1-1 Subgroup definitions

Subgroup variables	Categories	Description	Label for outputs	Suffix for outputs
Country	Participating countries[1]		Region	a
Randomization weight stratum	Body weight strata: <90 kg, ≥90 kg) and < Tertile 1, ≥ Tertile 1 and < Tertile 2, ≥ Tertile 2		Weight strata	b
Gender	Male, female		Gender	c
Age	< 65 years, ≥ 65 years and < 75 years, ≥ 75 years		Age	d
Smoking status	Current smoker, Current Non-smoker (i.e. never smoked or former smoked) at screening		Smoking status	e
PASI at baseline	PASI ≤ 20,PASI > 20		PASI category	f
BSA and PASI at baseline	Moderate psoriasis ((BSA ≥ 10% or PASI ≥ 10) and BSA ≤ 20% and PASI ≤ 20), severe psoriasis (BSA > 20% or PASI > 20)		Severity of psoriasis	g
Psoriatic Arthritis at Baseline	Yes, No		Psoriatic Arthritis	h
Previous psoriasis therapy	Yes, No Failure * (Yes, No)	Any previous psoriasis therapy discontinued within 5 years prior to Screening * at least one therapy with lack of efficacy or lack of tolerability	Previous psoriasis therapy	i

[1] Depending on the number of patients per country, some countries may be combined for the respective analyses

Table 1-2 Subgroup analyses

Endpoint/ analysis	Region	Weight strata	Gender	Age	Smoking status	PASI category	Severity of psoriasis	Psoriatic arthritis	Previous psoriasis therapy
Subject disposition	X								
Demography & baseline characteristics	X								
Study medication: duration of exposure	X								
Maintaining of PASI 90	X	X	X	X	X	X	X	X	X

Endpoint/ analysis	Region	Weight strata	Gender	Age	Smoking status	PASI category	Severity of psoriasis	Psoriatic arthritis	Previous psoriasis therapy
response									
PASI 50, 75, 90, 100 response at Week 52	X	X	X	X	X	X	X	X	X
AEs by SOC-PT	X	X							
SAEs by SOC-PT	X								
AEs study-drug related (investigators assessment)	X								

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

1.4.1 Assessment windows

At each visit, all study assessments should be completed prior to any potential application of the study treatment. Visit windows are described below.

1.4.2 Study Day 1 and other study days

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

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

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

The term “Day 0” will not be used.

1.4.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of visit 2. 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.

Visit 2 is defined as *Baseline* visit. All consecutive visits are labeled according to the pre-planned study week where they occur, i.e. *Week 1*, *Week 2*, and so on.

Week 24 is defined as the end of Treatment Period 1 (visit 11) for patients without premature discontinuation during Treatment Period 1. For patients with premature termination within Treatment Period 1 the last visit is defined as end of Treatment Period 1.

Week 52 is defined as the end of Treatment Period 2 (visit 18) for patients without premature discontinuation during Treatment Period 2. For patients with premature termination in Treatment Period 2 the last visit is defined as end of Treatment Period 2.

Any visits and assessments occurring after the end of Treatment Period 2 visit (Week 52 in the eCRF) will be aligned to the Week 60 Follow-Up visit.

1.4.4 Analysis 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. The visit windows for Treatment Period 1 and Treatment Period 2 are shown in Table 1-3. In this table, the days are counted since the first dose of study treatment (study days).

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified in Section 1.4.5.

Table 1-3 Analysis windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Analysis Window
Screening	-4 to BSL		-28 days to Day 1
Baseline*	BSL	1	
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-99
Week 16	16	113	Day 100-127
Week 20	20	141	Day 128-155
Week 24	24	169	Day 156-183**
Week 28	28	197	Day 184-211
Week 32	32	225	Day 212-239
Week 36	36	253	Day 240-267
Week 40	40	281	Day 268-295
Week 44	44	309	Day 296-323
Week 48	48	337	Day 324-351
Week 52	52	365	Day 352-379

* Baseline measurement before the first drug administration. The days are counted since the first dose of study treatment.

** Data assessed after the date of the Week 24 dose will not be considered as "Week 24 data"

For parameters which are not collected at every visit (e.g. DLQI, WPAI-PSO), visit windows defined in Table 1-3 will be combined. For example, if a parameter is measured at Week 24, Week 36 and Week 48, but not in between (i.e. Week 28, Week 32, Week 40 and Week 44), the Week 36 visit window will extend from Day 212 to Day 295 (combining Week 32 to Week 40 visit windows). If more than one assessment falls into the interval, the rules defined in Section 1.4.5 below are applied.

Assessments from Treatment Period 2 will not be considered for Treatment Period 1 and Treatment Period 1 visits will not be mapped into Treatment Period 2. For example, if a Week 28 (scheduled visit) measurement falls into the Week 20 visit window, this measurement would not be analyzed as Treatment Period 1 value.

1.4.5 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window.

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

- for *quantitative variables*, the *closest* to the actual visit is chosen. If two assessments have the same distance, then the earlier one will be chosen.

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

1.4.6 Day of last dose of study treatment

The date of last dose will be collected via the eCRF. The subject's extent of exposure will be calculated considering the end of treatment period visit (e.g., Treatment Period 1 completion visit). If a subject discontinued early, then the last visit during the treatment period is considered (e.g., last visit in Treatment Period 1, if subject discontinued from Treatment Period 1).

1.5 Subject disposition, background and demographic characteristics

1.5.1 Subject disposition

The total number of subjects screened and of subjects in the SAF-TP1 set will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of subjects in the SAF-TP1 who completed Treatment Period 1 and who discontinued the study prematurely (including the reason for discontinuation) in this period will be presented.

The number of patients in the SAF-TP2 and the numbers of patients in the FAS-P90R set and in the FAS-P75R set will be provided. The numbers and percentages of subjects in the FAS-P90R and in the FAS-P75R who completed Treatment Period 2 and who discontinued the study prematurely (including the reason for discontinuation) in this period will be presented. Furthermore, the numbers of patients in the PP-P90R, PP-FUS and in the FUS will be presented.

Reportable protocol deviations as defined in the final protocol deviation (PD) Edit Check Specification will be presented in terms of absolute numbers and percentages separately for each study period (Treatment Period 1, Treatment Period 2, Follow-Up Period) for the SAF-TP1, the FAS-P90R and the FAS-P75R.

1.5.2 Background and demographic characteristics

The following common background and demographic variables will be analyzed:

- Age (which is derived from date of birth and the date of screening visit)
- Age categories (<65 years, ≥ 65 years and < 75 years, ≥ 75 years)
- Gender
- Race

- Height
- Weight at Baseline
- Weight categories at Baseline (< 90kg, ≥ 90kg)
- Body mass index at Baseline (BMI)
- Smoking status at screening visit (never, current, former)
- Smoking amount: estimated amount consumed (in pack years) for current smokers
- Time since stop of smoking until screening visit (years)
- Tuberculosis (TB) status at Baseline (no TB present, active TB diagnosed, latent TB diagnosed)
- Initiation of TB therapy according to local guidelines (yes, no) for patients with latent TB

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

$$\text{BMI (kg/m}^2\text{)} = \text{(body weight in kilograms at V2) / (height in meters)}^2$$

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

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

- Baseline PASI
- Baseline PASI categories (≤ 20, > 20)
- Baseline IGA mod 2011 score (almost clear, mild disease, moderate disease, severe disease)
- Body Surface Area (BSA) affected by plaque-type psoriasis at baseline
- Time since occurrence of plaque psoriasis (years between start date and date of screening visit)
- Presence of psoriatic arthritis
    - time since occurrence of psoriatic arthritis (years between start date and date of screening visit)

Unless otherwise specified, summary statistics will be presented for continuous variables for all subjects in the SAF-TP1 and for each treatment group and for all subjects (total) in the FAS-P90R and the FAS-P75R.

The number and percentage of subjects in each category will be presented for categorical variables for all subjects in the SAF-TP1 and for each treatment group and for all subjects (total) in the FAS-P90R and the FAS-P75R.

Smoking history will be analyzed separately for former and current smokers. No statistical tests for comparability of baseline characteristics will be performed.

1.5.3 Medical history and current medical conditions

Analyses will be based on all subjects in the SAF-TP1 and on the FAS-P90R and the FAS-P75R by treatment group and overall.

Any condition entered on the *Relevant medical history/current medical conditions* eCRF will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary. *Cardiovascular medical history* will be summarized by the categories provided in the eCRF separately for prior and ongoing terms.

1.6 Study medication

The analysis of study treatment data during Treatment Period 1 will be based on the SAF-TP1 and during Treatment Period 2 on the FAS-P90R and the FAS-P75R.

The number of administered injections will be summarized for all patients in the SAF-TP1 and by treatment group in the FAS-P90R and the FAS-P75R according to the methods described in Section 2.1 (continuous data) and Section 2.2.1 (categorical data).

Compliance will be calculated in percent separately for both treatment periods, as the number of injections administered divided by the number of injections scheduled according to the protocol.

Duration of exposure will be defined as the time (in days) from first dose of study medication in a treatment period to the day of the last dose of study treatment in the respective treatment period (section 1.4.6).

The duration of exposure to study treatment will be summarized for all patients in the SAF-TP1 and by treatment group in the FAS-P90R and the FAS-P75R. In addition, the number of subjects with exposure of at least certain time thresholds will be displayed. The following categories will be presented for Treatment Period 1: “any exposure”, “≥1 week” (i.e. “≥7 days), “≥2 weeks” (i.e. ≥14 days), “≥3 weeks” (i.e. ≥21 days), “≥4 weeks” (i.e. ≥28 days), “≥8 weeks” (i.e. ≥56 days), “≥12 weeks” (i.e. ≥84 days), “≥16 weeks” (i.e. ≥112 days) and “≥20 weeks” (i.e. ≥140 days).

For Treatment Period 2 exposure categories in terms of 2-weeks intervals will be presented for the SAF-TP2: starting with “any exposure”, “≥2 weeks” (i.e. ≥14 days), “≥4 weeks” (i.e. ≥28 days) , “≥6 weeks” (i.e. ≥42 days), “≥8 weeks” (i.e. ≥56 days) up to “≥24 weeks” (i.e. ≥168 days).

The amount of observed “patient years” will be calculated as sum of all subject-times (in days) divided by 365.25 for both treatment periods.

1.7 Prior and concomitant medication

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code.

Prior and concomitant medications will be summarized in separate tables for all patients in the SAF-TP1 and by treatment group in the FAS-P90R and the FAS-P75R. In the SAF-TP1

concomitant medication will be only displayed for Treatment Period 1, in the FAS-P90R and FAS-P75R only concomitant medication from Treatment Period 2 will be presented.

Prior medications are defined as drugs taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of study treatment and the last day of Treatment Period 2 will be a **concomitant** medication, including those which were started pre-baseline and continued into the Treatment Period 1. Medication with start date prior to Baseline and without end date will be considered as concomitant medication. Medications starting at the last day of Treatment Period 1 will be considered as concomitant medication for Treatment Period 2. Incomplete start and/or stop dates (e.g. only the year) of medication are supposed to lie before the date of first dose of study treatment.

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 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.

Specific summaries of prior and/or concomitant medication will be presented for the categories of previous psoriasis therapy presented in Table 1-4.

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

Table 1-4 Categories of previous psoriasis therapy

Level 1 description	Level 1 outcome	Level 2 description	Level 2 outcome
previous psoriasis therapy	no		
	yes	number*	1
			2
			>=3
		failure**	no
			yes

only selected subgroups will be used for reporting

*: number of treatment (e.g. two treatment cycles with the same medication are counted twice)

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

1.8 Efficacy evaluation

1.8.1 Variables

The primary efficacy variable is the maintaining of PASI 90 response at Week 52 for patients with PASI 90 response at Week 24. The primary analysis of this primary variable will be based on the FAS-P90R.

Table 1-5 lists the primary, key secondary, secondary and exploratory variables for this study. The testing strategy for the analysis of the primary variable is described in Section 1.8.6.

Table 1-5 Primary, key secondary, secondary and exploratory efficacy variables as described in the protocol by treatment period

Variable	Type	Treatment Period
PASI 90 response at Week 52 for patients with PASI 90 response at Week 24	primary	TP2
PASI 90 response at Week 52 for patients with PASI 75 response but without PASI 90 response at Week 24	key secondary	TP2
PASI 50/75/100 response at Week 52	secondary	TP2
IGA mod 2011 0 or 1 response at Week 52	secondary	TP2
Time course of PASI from Week 24 to Week 52 and change of PASI compared to baseline [1]	secondary	TP2/FU[1]
Time course of DLQI from Week 24 to Week 52 and change of DLQI compared to baseline	secondary	TP2
Time course of DLQI 0 or 1 from Week 24 to Week 52	secondary	TP2
Time course of EQ-5D-5L from Week 24 to Week 52 and change of EQ-5D-5L compared to baseline	secondary	TP2
Time course of WPAI-PSO from Week 24 to Week 52 and change of WPAI-PSO compared to baseline	secondary	TP2
Time course of assessment of pain itching and scaling from Week 24 to Week 52 and change of this assessment compared to baseline	secondary	TP2
PASI 50, 75, 90 and 100 response at Week 24	exploratory	TP1
IGA mod 2011 0 or 1 response at Week 24	exploratory	TP1
Time to PASI 90 response from Week 24 on for patients with PASI 75 response but without PASI 90 response at Week 24	exploratory	TP2
Time to loss of PASI 75 response from Week 24 on for patients with PASI 75 response but without PASI 90 response at Week 24	exploratory	TP2
PK data and PASI response during course of the study	exploratory	TP1/TP2
Time to loss of PASI 90 response after Week 24 for patients with PASI 90 response at Week 24	exploratory	TP2
Time to loss of IGA mod 2011 0/1 response after Week 24	exploratory	TP2

1: for patients in the FAS-P75R also the Week 60 visit will be considered for this analysis

Additional efficacy endpoints not described in the protocol but included in the analysis are listed in Table 1-6.

Table 1-6 Additional efficacy variables not described in the protocol by treatment period

Variable	Type	Treatment Period
PASI 50/75/90/100 response from Week 24 to Week 48[1,2]	additional secondary	TP2/FU[2]
IGA mod 2011 0 or 1 response from Week 24 to Week 48[1,2]	additional secondary	TP2/FU[2]
Body Surface Area affected by plaque-type psoriasis at Week 52 and change from baseline	additional exploratory	TP2
Time course of PASI from Baseline to Week 24 and change of PASI compared to baseline	additional exploratory	TP1
PASI 50/75/90/100 response from Week 1 to Week 20	additional exploratory	TP1
IGA mod 2011 0 or 1 response from Week 1 to Week 20	additional exploratory	TP1
Time course of DLQI from Baseline to Week 24 and change of DLQI compared to baseline	additional exploratory	TP1
Time course of EQ-5D-5L Baseline to Week 24 and change of EQ-5D-5L compared to baseline	additional exploratory	TP1
Time course of WPAI-PSO from Baseline to Week 24 and change of WPAI-PSO compared to baseline	additional exploratory	TP1
Time course of assessment of pain, itching and scaling from Baseline to Week 24 and change of this assessment compared to baseline	additional exploratory	TP1
Relapse at Week 60	additional exploratory	FU
Rebound at Week 60	additional exploratory	FU

1: the analysis of this variable will be added to the respective analysis for Week 52
2: for patients in the FAS-P75R also the Week 60 visit will be considered for this analysis

An overview of statistical analyses and methods applied to efficacy variables is given in Table 1-7 .

Table 1-7 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Risk Difference	Logistic regression	Summary statistics for continuous data	Analysis of Co-variance	Time to event data analysis
PASI 90 response at Week 52 for patients with PASI 90 response at Week 24	X	X	X			
PASI 90 response at Week 52 for patients with PASI 75 response but without PASI 90 response at Week 24	X	X	X			
PASI 50/75/90/100 response from Week 28 to Week 52 (or Week 60)	X	X				
IGA mod 2011 0 or 1 response from Week 28 to Week 52 (or Week 60)	X	X				
Time course of PASI from Week 24 to Week 52 and change of PASI compared to baseline				X	X	
Time course of DLQI from Week 24 to Week 52 and change of DLQI compared to baseline				X	X	
Time course of DLQI 0 or 1 from Week 24 to Week 52	X	X				
Time course of EQ-5D-5L from Week 24 to Week 52 and change of EQ-5D-5L compared to baseline	X			X	X	
Time course of WPAI-PSO from Week 24 to Week 52 and change of WPAI-PSO compared to baseline				X	X	
Time course of assessment of pain itching and scaling from Week 24 to Week 52 and change of this assessment compared to baseline				X	X	
PASI 50, 75, 90 and 100 response at Week 24	X					
IGA mod 2011 0 or 1 response at Week 24	X					
Time to PASI 90 response from Week 24 on for patients with PASI 75 response but without PASI 90 response at Week 24						X
Time to loss of PASI 75 response from Week 24 on for patients with PASI 75 response but without PASI 90 response at Week 24						X
PK data and PASI response during course of the study						
Time to loss of PASI 90						X

Variable(s)	Summary statistics for binary/ categorical data	Risk Difference	Logistic regression	Summary statistics for continuous data	Analysis of Co-variance	Time to event data analysis
response after Week 24 for patients with PASI 90 response at Week 24						
Time to loss of IGA mod 2011 0/1 response after Week 24						X
Body Surface Area affected by plaque-type psoriasis at Week 52 and change from baseline				X		
Time course of PASI from Baseline to Week 24 and change of PASI compared to baseline				X		
PASI 50/75/90/100 response from Week 1 to Week 20	X					
IGA mod 2011 0 or 1 response from Week 1 to Week 20	X					
Time course of DLQI from Baseline to Week 24 and change of DLQI compared to baseline				X		
Time course of EQ-5D-5L Baseline to Week 24 and change of EQ-5D-5L compared to baseline				X		
Time course of WPAI-PSO from Baseline to Week 24 and change of WPAI-PSO compared to baseline				X		
Time course of assessment of pain itching and scaling from Baseline to Week 24 and change of this assessment compared to baseline				X		
Relapse at Week 60	X	X				
Rebound at Week 60	X	X				

1.8.1.1 Definition of total body surface area, PASI and related variables

The total body surface area (BSA) affected by plaque-type psoriasis is estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for full details of the PASI assessment). The following calculations will be done: Each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by chronic plaque psoriasis.

The PASI in Treatment Period 2 is assessed by a blinded PASI assessor without access to the randomization details. It is recommended that the same person performs all PASI assessments for a single patient.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) was derived as indicated in Table 1-8. 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 1-8).

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 PASI assessor was only responsible for collecting the components or scoring signs and total regional area and reported these data in a separate database. PASI calculations were done automatically within this system.

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

Table 1-8 The PASI scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = 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 based on the PASI and will be used for the efficacy evaluation in the current study:

- **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
- **Maintaining of PASI 90 response at Week 52**: maintaining of PASI 90 response at Week 52 is achieved for those subject from the FAS-P90R who achieved PASI 90 response as defined above at their Week 52 visit
- **PASI 100 response**: complete clearing of psoriasis (PASI=0)

- **Relapse**: when the achieved maximum PASI improvement from baseline is reduced by > 50%, i.e. relapse is defined as the following condition being fulfilled:

$$1 - \frac{D_i}{D^+_{max,i}} > 0.5$$

where D_i is the difference in PASI between Baseline and Week i and $D^+_{max,i}$ is the maximum improvement in PASI between Baseline and any visit prior to Week i.

- **Rebound**: A patient will be considered to have experienced a rebound, if the PASI increases to ≥125% of Baseline PASI, or if new pustular psoriasis, new erythrodermic psoriasis, or more inflammatory psoriasis occurs within 8 weeks after the last dose of study treatment has been received. For the current study rebound is assessed at the end of the Follow-Up period (i.e. Week 60 in the visit window described in Section 1.4.4).

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

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 1-9) has been developed based on a previous version of the scale used in AIN457 phase II studies, and has been updated in collaboration with health authorities. 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 1-9 The IGA mod 2011 rating scale

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

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

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

1.8.1.3 Health-related Quality of Life

The impact of psoriasis on various aspects of patients quality of life (HRQoL) was assessed by the following validated patient reported outcomes (PROs):

- Dermatology Life Quality Index (DLQI©)

- Patient's assessment of pain, itching and scaling
- European Quality of Life 5 Dimensions (EQ-5D)
- Work Productivity and Activity Impairment Questionnaire Psoriasis (WPAI-PSO)

Dermatology Life Quality Index (DLQI)

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". "Not relevant" is also a valid response. 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.

Patients assessment of pain, itching and scaling

Self-administered, 11-point numeric rating scales (NRS, 0-10) are used to evaluate the patient's assessment of their current pain, itching and scaling. Respondents answer the following questions for the assessment of:

- **Pain**: Overall, how severe was your psoriasis-related pain over the past 24 hours?
- **Itching**: Overall, how severe was your psoriasis-related itch over the past 24 hours?
- **Scaling**: Overall, how severe was your psoriasis-related scaling over the past 24 hours?

Patients have to rate their pain, itching, and scaling from 0 to 10 (11-point scale), with the understanding that the 0 represents the absence or null end of the pain, itching, or scale intensity (i.e., no pain, itching or scaling) and the 10 represents the other extreme of pain, itching, or scaling intensity (i.e., pain, itching or scaling as bad as it could be). The number that the patient selects represents his or her intensity score in the respective category.

European Quality of Live - 5 Dimensions (EQ-5D)

The EQ-5D is a non-disease specific, validated and widespread instrument for quantifying life quality of patients. The EQ-5D quantifies the health state of a patient for the following five dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In the current study the EQ-5D-5L version has been used which evaluates each of these dimensions using the following five labels: "no problems", "slight problems", "moderate problems", "severe problems" and "unable to/extreme problems".

Based on the five dimensions, a summary score (utility index) is derived using country specific value sets evaluating the patient condition described by the outcome in the single dimensions.

For the current analysis the EQ-5D-5L utility index based on the crosswalk value sets available from the EuroQol for Germany and for UK (http://www.euroqol.org/about-eq-5d/valuation-of-eq-5d/eq-5d-5l-value-sets.html) will be calculated and presented separately.

Additionally, a visual analogue scale (VAS) is used within the EQ-5D. This scale records the respondent's self-rated health on a vertical 20-cm VAS where the endpoints are labeled "best imaginable health state "and "worst imaginable health state." This results in a numeric value set ranging from 0 (="worst imaginable health state") up to 100 (="best imaginable health state").

Work Productivity and Activity Impairment Questionnaire Psoriasis (WPAI-PSO)

The WPAI-PSO is a self-administered questionnaire comprising of six questions about effects of psoriasis on the patient's ability to work and perform regular activities based on their experiences in the previous 7 days. The questionnaire quantifies the number of hours that the respondent was unable to work and, using a 10-point scale, evaluates the extent to which the respondent's psoriasis affected their productivity while working. For respondents who are not in paid employment, the questionnaire evaluates the extent to which the respondent's psoriasis affects their ability to perform regular daily activities.

The WPAI-PSO consists of six questions:

Q1 = currently employed

Q2 = hours missed due to health problems

Q3 = hours missed due to other reasons

Q4 = hours actually worked

Q5 = degree health affected productivity while working

Q6 = degree health affected productivity in regular unpaid activities.

The recall period for the questions 2 to 6 is seven days. Four main outcomes can be generated from the WPAI-PSO and expressed in percentages:

- % Absenteeism: percent work time missed due to health for those who were currently employed (i.e., only patients with Q1=Yes)
- % Presenteism: percent impairment while working due to health for those who were currently employed and actually worked in the past seven days (i.e., only patients with Q1=Yes)
- % Total work productivity impairment: percent overall work impairment due to health for those who were currently employed (i.e., only patients with Q1=Yes)
- % Total activity impairment: percent activity impairment due to health for all respondents

The percentage of impairment while working (presenteism) is calculated as Q5/10 x 100%. The percentage of work time missed (absenteeism) is calculated as Q2/(Q2 + Q4) x 100%. The percentage of total work productivity impairment (i.e., work productivity loss) is (Q2/(Q2 + Q4) + (1–Q2/(Q2+Q4)) x (Q5/10)) x 100%. The percentage of total activity impairment is

calculated as Q6/10 x 100%. In case of missing items the respective outcomes where these items are utilized cannot be calculated.

1.8.2 Statistical hypothesis, model, and method of analysis

The statistical null-hypothesis to be rejected in the primary analysis is that the odds ratio of maintaining a PASI 90 response for patients with secukinumab 4-weekly dosing versus patients on secukinumab 6-weekly dosing exceeds the non-inferiority margin of 1+δ.

The primary hypothesis is stated as follows:

Let π_j denote the probability of a PASI 90 response at Week 52 for dosing group j, j=0, 1, where

- 0 corresponds to 4-weekly dosing
- 1 corresponds to 6-weekly dosing

The following hypothesis will be tested

$$H_{01}: (\pi_0 /(1- \pi_0))/ (\pi_1 /(1- \pi_1)) \geq 1+\delta \text{ versus } H_{A1}: (\pi_0 /(1- \pi_0))/ (\pi_1 /(1- \pi_1)) < 1+\delta$$

The non-inferiority margin $1+\delta$ is calculated as 2.23 assuming a PASI 90 response maintenance rate of 81.8% under 4-weekly dosing treatment scheme and using a 15% non-inferiority margin. The **primary analyses** will be performed comparing dosing groups (Group 1 vs. Group 2) with respect to the primary efficacy variable in a logistic regression model with the factors dosing group, country, PASI 90 response at Week 16 (Yes, No) and body weight at Week 24 (< 90 kg or ≥ 90 kg, for model definition see Section 2.2.2). The odds ratios and their two-sided 95%-Wald confidence intervals (CIs) will be given.

In case of subgroup analyses where the grouping variable is one of the above described factors in the logistic regression model the respective factor is excluded from the model.

Additionally, the one-sided p-value for the shifted null-hypothesis will be given. The respective test statistic is calculated as

$$\frac{\hat{\beta}-\beta_0}{se_{\hat{\beta}}}$$

where $\hat{\beta}$ is the type 3 maximum likelihood estimate of the dosing group parameter in the logistic regression model and $se_{\hat{\beta}}$ is its standard error. β_0 is the non-inferiority margin of the estimator which corresponds to the δ from the above null-hypothesis and is therefore set to $ln(1+\delta)= ln(2.23) = 0.80$.

Only in case that the number of patients with response (or non-response) in one of the groups is 5 or lower, exact logistic regression will be used for the primary analysis instead of logistic regression using maximum-likelihood based estimators.

The primary analysis set will be the FAS-P90R.

1.8.3 Handling of missing values/discontinuations

Patients who drop out prematurely and/or do not have a valid PASI assessment at Week 52 will be counted as non-responders. Patients with major protocol violations, but with a valid PASI assessment will be included in the intention-to-treat (ITT)-analysis (i.e. primary analysis) with their observed response. The same algorithm will be used for the key secondary endpoint, the PASI 90 response at Week 52 in the FAS-P75R set. Missing values for secondary endpoints or other outcomes (e.g. quality of life, safety or lab measurements) will not be replaced.

1.8.4 Supportive analyses

Sensitivity analyses for the primary outcome will be performed as follows:

(A) In addition to the logistic regression model the risk difference for PASI 90 response at Week 52 between Group 1 and Group 2 will be computed with the corresponding 95%-CI (asymptotic Wald CIs with continuity correction) using the SAS PROC FREQ procedure with the RISKDIFFC option.

(B) The primary analysis (logistic regression analysis) and the analysis of risk difference will be repeated for the PP-P90R set.

(C) An analysis based on multiple imputations of the PASI 90 response at Week 52 will be performed. Details are described in Section 2.2.3.

1.8.5 Key secondary analyses

Aim of the key secondary analysis, the PASI 90 response rate at Week 52 in the FAS-P75R, is the demonstration of superiority of the shortened 2-weekly dosing group compared to the 4-weekly dosing group in this patient set.

The statistical null-hypothesis to be rejected is that the odds ratio of gaining a PASI 90 response for patients on 2-weekly dosing versus patients on 4-weekly dosing = 1.

Let π_j denote the probability of a PASI 90 response at Week 52 for treatment group j, j=0, 1, where

- 0 corresponds to 2-weekly dosing
- 1 corresponds to 4-weekly dosing

The following hypothesis will be tested

$$H_{02}: (\pi_0 /(1- \pi_0))/ (\pi_1 /(1- \pi_1)) = 1 \text{ versus } H_{A2}: (\pi_0 /(1- \pi_0))/ (\pi_1 /(1- \pi_1)) \neq 1$$

This analysis will be performed comparing dosing groups (Group 3 vs. Group 4) with respect to the key secondary variable in a logistic regression model with the factors dosing group, country, body weight at Week 24 (< 90 kg or ≥ 90 kg) and PASI response (<83% vs. ≥83%) at Week 24. The odds ratio with its corresponding 95%-Wald CI and the (two sided) p-value of the corresponding Wald statistic will be presented.

In case of subgroup analyses where the grouping variable is one of the above described factors in the logistic regression model the respective factor is excluded from the model.

1.8.6 Testing strategy of the primary and the key secondary analysis

Significance Level: The primary analysis will be performed at the one-sided 2.5% level which corresponds to a two sided 5% level. Non-inferiority of 6-weekly vs. 4-weekly dosing will be claimed, if the upper limit of the two sided 95%-Wald CI for the odds ratio estimated in the above described logistic regression model does not exceed 2.23.The key secondary analysis will be performed on the two-sided 5% level of significance. The test decision will be based on the Wald test, i.e. if the p-value from the test is below 0.05.

Multiplicity issues: The key secondary analysis will be included in the confirmatory testing strategy using a hierarchical testing strategy. The key secondary hypothesis will be a priori ordered below the primary hypothesis. This means that no multiplicity adjustment of the significance level is required; however, confirmatory evidence will be claimed only if non-inferiority with regard to the primary endpoint has been successfully demonstrated before. Otherwise, the result for the secondary endpoint will be interpreted as being purely explorative, independent of the nominal p-value.

1.8.7 Secondary analyses

All secondary efficacy analyses for Treatment Period 2 (and Week 60, if applicable) will be performed by dosing group in the FAS-P90R and the FAS-P75R, separately.

PASI 50/75/90/100 and IGA mod 2011 0 or 1 response over time in Treatment Period 2 and Follow-Up Period

Summary statistics for PASI 50/75/90/100 response and for IGA mod 2011 0 or 1 response from Week 24 to Week 52 will be presented for the FAS-P90R and the FAS-P75R separately in contingency tables including absolute and relative frequencies. For the FAS-P75R also the response rates at Week 60 will be provided. Risk differences between the dosing groups will also be provided.

Figures will be provided as well displaying estimates for responder rates by dosing group.

PASI score over time in Treatment Period 2 and Follow-Up Period

Summary statistics will be provided for absolute PASI scores as well as for absolute and percent change from baseline by visit and treatment group. The analysis will be performed until Week 52 in the FAS-P90R and until Week 60 for the FAS-P75R. Figures for mean course of the PASI score will also be provided.

The absolute PASI score will be analyzed by analysis of covariance (ANCOVA) models with dosing group, country and body weight stratum as explanatory variables and baseline value as covariate. ANCOVAs will be performed at each visit starting with Week 28.

DLQI, EQ-5D, WPAI-PSO and assessment of pain, itching and scaling in Treatment Period 2

For the DLQI subscale and the DLQI total score, the EQ-5D VAS and the EQ-5D utility index, for each of the main outcomes of the WPAI-PSO and for the assessment of pain, itching and scaling, the absolute and percentage change from baseline to each visit during

Treatment Period 2 where the scales are assessed will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and dosing group.

ANCOVA models with dosing group, country and body weight stratum as explanatory variables and baseline value as covariate will be performed for the visits Week 36, 48 and 52.

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1 at each visit where the DLQI is assessed. Risk differences including 95%-CIs will also be presented for the visits Week 36, 48 and 52.

For the single EQ-5D dimensions contingency tables will be provided for each visit where the scale was to be assessed. Changes from baseline to each visit will be displayed using the categories *improved*, *unchanged* and *worsened* in each dimension.

1.8.8 Exploratory analyses

All exploratory efficacy analyses for Treatment Period 2 will be performed by dosing group in the FAS-P90R and the FAS-P75R, separately. Exploratory analyses for Treatment Period 1 will be performed in the SAF-TP1. Analyses for Week 60 (rebound and relapse) will be based on the FUS.

PASI and IGA mod 2011 0 or 1 response in Treatment Period 1

Summary statistics will be provided for absolute PASI scores in Treatment Period 1 as well as for absolute and percent change from baseline by visit.

Contingency tables for PASI 50/75/90/100 and IGA mod 2001 0 or 1 response in Treatment Period 1 will be presented by visit starting with Week 1 and will include absolute and relative frequencies.

DLQI, EQ-5D, WPAI-PSO and assessment of pain, itching and scaling in Treatment Period 1

For the DLQI subscale and the DLQI total score, the EQ-5D VAS and the EQ-5D utility index, for each of the main outcomes of the WPAI-PSO and for the assessment of pain, itching and scaling, the absolute and percentage change from baseline to week 4, 12 and 24 will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit.

For the single EQ-5D dimensions contingency tables will be provided for each visit where the scale was to be assessed. Changes from baseline to each visit will be displayed using the categories *improved*, *unchanged* and *worsened* in each dimension.

Time to event analyses for PASI and IGA mod 2011 0 or 1 during Treatment Period 2

Kaplan-Meier analyses, log-rank tests and Cox proportional Hazard models will be performed for all time to event analyses in Treatment Period 2 with respect to the respective dosing groups in the analysis set. Further specifications of the applied statistical methods are provided in Section 2.3.

The analysis of time to PASI 90 response and the analysis of time to loss of PASI 75 response will be conducted in the FAS-P75R set, the analysis of time to loss of PASI 90 response in the FAS-P90R. The time to loss of IGA mod 2011 0 or 1 response will be performed in both patient sets for patients with IGA mod 2011 0 or 1 response at Week 24.

Body Surface Area affected by plaque-type psoriasis at Week 52

The absolute and percentage change from baseline to Week 52 will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit for the FAS-P90R and the FAS-P75R.

Relapse and Rebound at Week 60

Contingency tables including absolute and relative frequencies will be provided for relapse and rebound at Week 60 in the FUS and in the PP-FUS. Risk differences including 95%-CIs between the (former) dosing groups, i.e. Group 3 vs. Group 4, will also be presented.

Association between PK data and PASI response during course of the study

1.8.9 These evaluations are not part of the current analysis plan. Resource utilization

Data relating to resource utilization might be used for the purpose of economic evaluations. However, these evaluations are not part of the current analysis plan.

1.8.10 Pharmacokinetics

Analysis of pharmacokinetic (PK) data will be performed separately for Treatment period 1 and Treatment Period 2. All subjects from the respective Safety Set (SAF-TP1 and SAF-TP2) with quantifiable PK measurements of secukinumab will be included in the PK data analysis. Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings. PK concentrations will be summarized by visit and, in Treatment Period 2, by treatment group. In addition to the overall summaries, PK concentrations will be provided by PASI response: in Treatment Period 1 the summary will be stratified by PASI response at Week 24 (PASI 90, PASI 75 to 90, below PASI 75), in Treatment Period 2 by PASI 90 response at Week 52. For the stratification by PASI response only subjects with a PASI assessment at Week 24 or Week 52, respectively, will be considered.

In addition to mean, standard deviation (SD), coefficient of variation (CV), median and quartiles, the geometric mean and geometric coefficient of variation (CV) and n(log) will be presented. The formula for deriving the geometric mean and CV (%) is as following:

- CV (%) = (SD/mean)*100,
- geometric mean=exp((sum of log transformed data) / number of non-missing data points after log transformation),
- geometric CV = sqrt(exp(variance of log-transformed data)-1)*100.

In addition, sample number, concentration, sample date, sample time at pre-dose and minutes pre-dose will be listed by treatment sequence.

Values below lower limit of quantification/below detection limit will be imputed by 0.

Additionally, the geometric mean values during Treatment Period 1 will be displayed graphically stratified by PASI response at Week 24 (PASI 90, PASI 75 to 90, below PASI 75). Figures of the geometric means during Treatment Period 2 will be provided within each treatment group and stratified by PASI response at Week 52. For these figures only subjects with a PASI assessment at Week 24 or Week 52, respectively, will be considered.

1.9 Standard safety evaluation

Safety analyses will be performed separately for Treatment Period 1, Treatment Period 2 and the Follow-Up period. Additionally, adverse events will be analyzed for the Entire Study Period combined (i.e. Treatment Period 1, Treatment Period 2).

Safety analyses for Treatment Period 1 will be based on the SAF-TP1, for Treatment Period 2 on the SAF-TP2, analyses for the post treatment Follow-Up period on the FUS and analyses for the Entire Treatment Period on the SAF-TP1.

Treatment groups for evaluation of Treatment Period 2

For safety-evaluations, the patient groups of PASI 90 responders and those who achieve PASI 75 but not PASI 90 will be pooled for Group 1 and Group 3; therefore, only 3 dosing groups will be analyzed in Treatment Period 2:

- Secukinumab 300 mg s.c. every 2 weeks (patients from Group 4).
- Secukinumab 300 mg s.c. every 4 weeks (patients from Group 1 pooled with Group 3).
- Secukinumab 300 mg s.c. every 6 weeks (patients from Group 2).

Additionally, the total number of patients over all groups will be analyzed in a separate column. Patients will be analyzed according to the treatment regimen they received.

If the treatment regimen of patients only deviates partially from the randomized treatment regimen during Treatment Period 2, these patients will be analyzed according to the treatment randomized.

Treatment groups for evaluation of Follow-Up Period

For the analysis of the post treatment Follow-Up Period Group 3 and Group 4 defined in Section 1.2 will be used next to a combined group.

Treatment groups for evaluation of Entire Treatment Period

For the evaluation of the Entire Treatment Period all patients in the SAF-TP1 will be analyzed without consideration of any treatment groups.

1.9.1 Adverse events

For adverse events and other binary safety variables crude incidence rates and associated 95%-CIs will be derived.

The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Only primary paths within MedDRA will be considered for AE reporting.

Treatment emergent adverse events are AEs which 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 during the Treatment Period 1, Treatment Period 2 or Follow-Up Period.

The assignment of an AE to a specific treatment period is according to its start date: an AE with start date in Treatment Period 1 and ongoing in Treatment Period 2 will count for Treatment Period 1. Only in case of increased severity in Treatment Period 2 it will also count for Treatment Period 2.

AEs will be summarized by presenting, for each treatment group (including "any AIN457"), the number and percentage of subjects having at least one AE, having an AE in each primary SOC and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs, i.e. AEs for which a possible causal relationship to the study drug has been stated in the eCRF. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries.

If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. The same algorithm applies to study treatment related AEs.

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

Separate summaries will be provided for deaths, serious adverse events and adverse events leading to study drug discontinuation.

The adverse events will be summarized as crude incidence rates by subgroup as indicated in Table 1-1.

Non-treatment emergent adverse events will be summarized as well. These adverse events occurring before the first dose of the study treatment will be listed.

Separate summaries will be provided for liver-related adverse events and liver-related adverse events where causal relationship to study treatment at least cannot be excluded. Liver events are defined in the protocol and reported in the eCRF.

1.9.2 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, clinical chemistry and urinalysis). The results will be provided separately for each study period by study visit and treatment group using the treatment groups defined in Section 1.9.

Descriptive summary statistics for the change from baseline to each study visit will be presented by laboratory test and treatment group for all non-categorical parameters. Change

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

change from baseline = post baseline value – baseline value

Clinically notable laboratory values will be analyzed for the following laboratory parameters with respect to the criteria given in Table 1-10: alanine aminotransferase (ALT), aminotransferase (AST), total bilirubin (TBL), alkaline phosphatase (ALP), creatinine (serum), potassium, sodium, hemoglobin (HGB), platelets, white blood cell count, neutrophils, eosinophils, lymphocytes and protein urine. The number and percentage of subjects with clinically notable laboratory value newly occurring or worsening after baseline will be presented. These summaries will be split into *liver function and related variables*, *renal function and electrolyte variables*, *hematology variables* and *urinalysis variables*.

Table 1-10 Criteria for notable laboratory parameters to be analyzed

Variable	Criterion for notable value
Liver function and related variables	
ALT increased	>3.0 x Upper Limit of Normal (ULN)
AST increased	>3.0 x ULN
Total bilirubin (TBL) increased	>2.0 x ULN
ALP increased	>2.5 x ULN
Renal function and electrolyte variables	
Creatinine increased	>1.5 x ULN
Potassium abnormal	> 6 mmol/L or <3 mmol/L
Sodium abnormal	>160 mmol/L or < 115 mmol/L
Hematology variables	
HGB decreased	≥20 g/L decrease from Baseline
Platelet count decreased	< Lower Limit of Normal (LLN)
White blood cell decreased	<0.8 x LLN
Neutrophil decreased	<0.9 x LLN
Eosinophils increased	>1.1 x ULN
Lymphocytes increased	>1.1 x ULN
Urinalysis variable	
Protein urine dipstick	≥ 100 mg/dL (++)

The number and percentage of subjects with notable laboratory value newly occurring or worsening after baseline will be presented.

Newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 1-11. For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g., a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5x ULN.

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

Table 1-11 Liver-related events

Parameter	Criterion
ALT or AST	>3xULN; >5xULN
TBL	>1.5xULN; >3xULN,
ALP	>2xULN; >5xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP ≤2xULN **(Hy's Law)**

1.9.3 Vital signs

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

change from baseline = post-baseline value – baseline value

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

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

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 1-12 below.

Table 1-12 Criteria for notable vital sign abnormalities

Description of abnormality	Notable abnormalities
Hypertension	Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg
Hypotension	Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg
Abnormal pulse	> 100 bpm or <60 bpm

1.9.4 Electrocardiogram (ECG)

The following quantitative variables will be summarized: RR interval, PR interval, QRS duration, QT interval (QT), corrected QT interval using Fredericia's formula (QTcF) and heart rate (HR).

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

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

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 result at Week 24 and at Week 52 (normal, abnormal, not available, total) will be provided.

A listing of all newly occurring or worsening abnormalities will be provided.

1.10 Compound specific safety evaluation

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

AEs of special interest (AESI) will be analyzed separately for Treatment Period 2 and the Entire Treatment Period. Crude incidence rates and corresponding confidence intervals of AESI will be summarized overall and by PT.

In addition, listings will be provided presenting which subjects experienced which risk.

The following AESI are part of the analysis.

- Major adverse cardiovascular events (MACE): identified per Novartis MedDRA Query (NMQ) "MACE (MI, Stroke, Cardiovascular death)"
- Inflammatory bowel disease: identified per NMQ "Inflammatory bowel disease"
- Candida infections: any AE with Candida high level term
- Malignancy: identified per NMQ "Malignant or unspecified tumours (excl. BCC and SCC)"
- Hypersensitivity and injection site reaction: identified per SMQ "Hypersensitivity"
- Hepatotoxicity: identified per SMQ "Drug related hepatic disorder - severe events only"

1.11 Sample size calculation

Based on the pooled data from the CAIN457A program (CAIN4572302 and CAIN4572303), the PASI 90 response rate for biologics-naïve patients treated with AIN457 300 mg s.c. was 74.3% at 24 weeks. Of those who were PASI 90 responders at Week 24, 81.8% of patients maintained their PASI 90 response until Week 52.

It was assumed that a dosing frequency of 6 weeks (Group 2) will differ in PASI 90 response up to 7% worse compared a dosing frequency of 4 weeks (Group 1). This assumption of a difference of maximally 7% is based on simulation of the PK levels obtained with maintenance treatments of AIN457 300 mg every 6 weeks and the correlation between plasma levels and the clinical response seen in the AIN457 Phase 3 studies.

A total of 554 patients per group are required to achieve 90% power on a one-sided, 2.5% significance level to demonstrate the non-inferiority of 6-weekly vs. 4-weekly dosing, if the true maintenance rates are 81.8% under 4-weekly and 74.8% under 6-weekly dosing and the non-inferiority margin is predefined as -15%.

The response rates underlying this estimation were obtained from pooled data of studies analyzed according to the ITT-principle using the same algorithm to handle drop-outs or protocol violations as in this present study. Therefore, the effect of drop-outs or protocol violations should be already accounted for in the effect estimates and no further adjustments of the sample size are required. However, to account for the fact that there might be minor differences (e.g. with respect to drop-out rates) between the historical data and the data to be observed in this study, the sample size was rounded up slightly to 570 patients/group who were to be randomized to Group 1 or Group 2 (giving a total of 1140 patients in both groups) of this study.

Assuming a PASI 90 response rate of 74% at Week 24, 1580 patients were to be enrolled at baseline in this study in order to achieve the required sample size for randomization at Week 24. This number still allows for some drop-out patients or patients withdrawing consent at or after randomization even after experiencing a PASI 90 response.

1.12 Interim analyses

No interim analysis was planned or performed for this study.

2 Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

If not otherwise specified, p-values will be presented as two-sided p-values, and two-sided confidence intervals will be displayed. For all tests the level of significance will be set to 5%.

2.1 Analysis of continuous data

2.1.1 Summary statistics for continuous data

The following summary statistics will be provided for continuous data by visit and dosing group (if applicable): N, mean, standard deviation, minimum, median, maximum.

2.1.2 Analysis of variance/covariance

Analysis of covariance (ANCOVA) will be used with dosing group, country and body weight stratum as explanatory variables and baseline value as covariate. In general, SAS Type III sums of squares will be utilized.

Difference between dosing groups will be determined using least-square means (LSMs) and t-tests using the pooled error term from the linear model. 95% percent CIs for the treatment difference will be calculated based on differences in LSM estimates.

2.2 Analysis of binary (and categorical) data

2.2.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If applicable, risk differences will be calculated

with a corresponding two-sided 95%-CI (asymptotic Wald CIs with continuity correction) using the SAS PROC FREQ procedure with the RISKDIFFC option.

2.2.2 Logistic regression

The analysis of the primary endpoint and of the key secondary endpoint will be performed using logistic regression models with factors dosing group, country and body weight at Week 24 (<90 kg or ≥90 kg). Potential further covariates in the model are specified in Section 1.8.2 and Section 1.8.5. Odds ratios will be computed for comparisons of secukinumab dosing regimens utilizing the logistic regression model fitted.

The odds ratios and their two-sided 95%-Wald confidence intervals will be computed utilizing the logistic regression model fitted. P-values will be given according to the descriptions in Section 1.8.2 and Section 1.8.5.

In case of subgroup analyses where the grouping variable is one of the above described factors in the logistic regression model the respective factor is excluded from the model.

The SAS procedure PROC LOGISTIC will be used for calculating logistic regression models. Dummy-coding will be performed with treatment reference category being *300 mg secukinumab every 4 weeks*.

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

1. Run the PROC LOGISTIC procedure with EXACT statement;
2. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with removing country, followed by weight stratum and PASI 90 response at Week 16
3. If convergence not reached, perform Fisher's exact test.

2.2.3 Multiple imputations for response variables

Non-responder imputation as primary analysis will be performed since low drop-out rates are expected. It is expected that subjects will be likely to drop-out due to lack of efficacy, such that a non-responder imputation will be reasonable.

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

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

Missing values for the 'change from baseline PASI score' will be imputed based on an underlying joint normal distribution and using a Markov Chain Monte Carlo (MCMC) method. The change from baseline in PASI score appears to follow closer to a normal distribution than the actual PASI score.

The imputations will be done separately for each dosing group including weight at Week 24 (in groups) as additional covariate. Values post assessment timepoint of the primary endpoint will not be considered for imputations.

The number of imputations will be set to 50, the seed for the random function will be set to 4573302 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 score as well as all changes from baseline PASI starting with Week 28.

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=miinfo_msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi> OUT=<impdata> SEED=4573302 NIMPUTE=50;
 VAR <weight at Week 24> >
     <baseline PASI>
     <change from baseline PASI week 24> - <change from baseline PASI week primary endpoint>;
  BY <dosing group>;
RUN;
ODS LISTING;
```

Two outputs will be prepared displaying i) the missing data patterns and the group means as stored in the data set msgpat and ii) the variance information and estimated means with confidence interval and range based on data sets varinfo and param which need to be merged by <dosing group>.

Programming notes:

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

The imputed data are saved in data set <impdata>. The outcome of interest, i.e. the PASI 90 response will be calculated as follows:

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

The treatment differences for each imputed data set will then be evaluated by means of logistic regression models as described in Section 2.2.2. This analysis will be done by

IMPUTATION for the comparison to the control group. A data set containing the estimated parameters of the logistic regression will be created (`ods output ParameterEstimes=lgsparms`).

The estimates based on the 50 imputed data are then combined by applying Rubin's rules for multiple imputed data sets, see Little and Rubin (2002). For this estimation the SAS procedure MIANALYZE will be used (`parms=lgsparms, modeleffects <Treatment group>`). ODS OUTPUT data sets containing ParameterEstimates, VarianceInfo and ModelInfo will be produced.

The data set ParameterEstimates contains the estimate for the log(odds ratio) and the lower and upper confidence intervals. These three variables will be back-transformed and presented in the results.

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

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

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

2.3 Analysis of time-to-event data

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

For each time-to-event variable, between-treatment differences will be evaluated using a log-rank test, stratified by country and weight at Week 24 (<90 kg or ≥90 kg) to compare the survival functions between the dosing groups. The hazard ratios for these comparisons for the variable and their corresponding 95% confidence intervals will be computed using a stratified, Cox proportional hazards regression model with dosing group and baseline PASI as explanatory variable and stratified by country and weight at Week 24. The SAS procedure PHREG, with option STRATA if applicable, will be used to perform the analysis. The Kaplan-Meier estimates of the survival functions for each treatment will be plotted. The plot will include the number of subjects at risk for each treatment group at pre-specified timepoints (e.g., visits). Median time to event and quartiles including 95% confidence intervals will be provided. The confidence intervals will be based on log-log transformation. (PROC LIFETEST option conftype=log-log; default in SAS 9.2). In addition, for pre-specified time intervals the following will be presented in an output:

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

The pre-specified time intervals for Treatment Period 2 are as follows: "≤4 weeks", ">4 weeks to ≤8 weeks", ">8 weeks to ≤12 weeks", ">12 weeks to ≤16 weeks", ">16 weeks to ≤20 weeks", ">20 weeks to ≤24 weeks", ">24 weeks to ≤28 weeks" and ">28 weeks".

Subjects at risk, timepoint "0" and censoring will be defined as described in Table 2-1 below.

Table 2-1 Time to event: definition of risk set, timing and censoring by variable

Variable: Time to	Risk set	Time = 0	Time of event	Censoring	Psoriasis ConMed	Informative censoring
PASI 90 response	FAS-P75R	Date of randomi-zation (Week 24)	Date of 1st visit with PASI 90 response observed	End of Treatment Period 2 (Week 52 visit)	Censor (if ConMed taken before the event)	No
Loss of PASI 90 response	FAS-P90R	Date of randomi-zation (Week 24)	Date of 1st visit with OBSERVED loss of PASI 90 response (i.e. no imputation for missing values)	End of Treatment Period 2 (Week 52 visit)	Event (if the subject took psoriasis ConMed, the subject is considered as having lost response)	Study phase discontinu-ation with reason "lack of efficacy"
Loss of PASI 75 response	FAS-P75R	Date of randomi-zation (Week 24)	Date of 1st visit with OBSERVED loss of PASI 75 response (i.e. no imputation for missing values)	End of Treatment Period 2 (Week 52 visit)	Event (if the subject took psoriasis ConMed, the subject is considered as having lost response)	Study phase discontinu-ation with reason "lack of efficacy"
Loss of IGA mod 2011 0 or 1 response	- All IGA 0 or 1 responders at Week 24 in FAS-P90R - All IGA 0 or 1 responders at Week 24 in FAS-P75R	Date of randomi-zation (Week 24)	Date of 1st visit with OBSERVED loss of IGA mod 2011 0 or 1 response (i.e. no imputation for missing values)	End of Treatment Period 2 (Week 52 visit)	Event (if the subject took psoriasis ConMed, the subject is considered as having lost response)	Study phase discontinu-ation with reason "lack of efficacy"

ConMed: Concomitant medication
Psoriasis ConMed is defined in MAP appendix

Time-to-event will be derived as:

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

3 References

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Approval of final RAP 3 document

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Date

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Signature