NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457A2325 / NCT03589885

Multicenter, rAndomized, double-blind, placebo-conTrolled, 52-week stUdy to demonstRatE the efficacy, safety and tolerability of subcutaneous secukinumab injections with 2 mL auto-injectors (300 mg) in adult subjects with moderate to severe plaque psoriasis – MATURE

Statistical Analysis Plan (SAP)

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23-Nov-2018	*Prior to FPFV*	*Creation of final version 1.0*	*First version*	*NA*

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List of abbreviations

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

WBC	White blood cell

1 Introduction

Data will be analyzed by Novartis according to the data analysis section 12 of the study protocol which is available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

This document covers statistical and analytical plans for CAIN457A2325 (MATURE) study with reference to the study protocol and the project standard analysis plans (AIN457A Master Analysis Plan).

1.1 Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in approximately 120 subjects with moderate to severe plaque-type psoriasis.

Randomization: Eligible subjects will be randomized using a 2:2:1:1 ratio into one of the following 4 treatment arms. In order to achieve a balanced weight distribution in each treatment arm, randomization in these four groups will be stratified by body weight at baseline (< 90 kg or ≥ 90 kg). • Group 1: Secukinumab 300 mg (2 mL AI): one 2 mL secukinumab 300 mg AI plus two 1 mL PFS matching placebo secukinumab s.c. injections once weekly at Randomization, Weeks 1, 2, and 3, followed by dosing every four weeks, starting at Week 4 and until Week 48, except for weeks 13, 14, and 15 where subjects will self-administer two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections.

• Group 2: Secukinumab 300 mg (2 x 1 mL PFS): two 1 mL secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections once weekly at Randomization, Weeks 1, 2, and 3, followed by dosing every four weeks, starting at Week 4 and until Week 48, except for weeks 13, 14, and 15 where they will self-administer a weekly dose of the two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections.

• Group 3: Placebo - Secukinumab 300 mg (2 mL AI): placebo treatment administered as two 1 mL placebo secukinumab plus one 2 mL AI matching placebo secukinumab s.c. injections once weekly at Randomization, Weeks 1, 2, and 3, followed by dosing every four weeks starting at week 4 till week 8. Prior to receiving the Week 12 dose, PASI 90 response will be evaluated. PASI 90 responders will receive placebo every four weeks from week 12 till week 48, except for weeks 13, 14, and 15 subjects will self-administer a weekly dose of two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections. The PASI 90 non-responders will be assigned to Secukinumab 300 mg (2 mL AI) group and receive their treatment every four weeks from week 12 till week 48, except for weeks 13, 14, and 15 where the patients will self-administer a weekly dose of the Secukinumab 300 mg (2 mL AI) group treatment.

• Group 4: Placebo - Secukinumab 300 mg (2 x 1 mL PFS): placebo treatment administered as two 1 mL placebo secukinumab plus one 2 mL AI matching placebo secukinumab s.c. injections once weekly at Randomization, Weeks 1, 2, and 3, followed by dosing every four weeks till week 8. Prior to receiving the Week 12 dose, PASI 90 response will be evaluated. PASI 90 responders will receive placebo every four weeks from week 12 till week 48, except

for weeks 13, 14, and 15 subjects will self-administer a weekly dose of two 1 mL placebo secukinumab 150 mg PFS plus one 2 mL AI matching placebo secukinumab s.c. injections. The PASI 90 non-responders will be assigned to Secukinumab 300 mg (2 mL PFS) group and receive their treatment every four weeks from week 12 till week 48, except for weeks 13, 14, and 15 where the patients will self-administer a weekly dose of the Secukinumab 300 mg (2 mL PFS) group treatment.

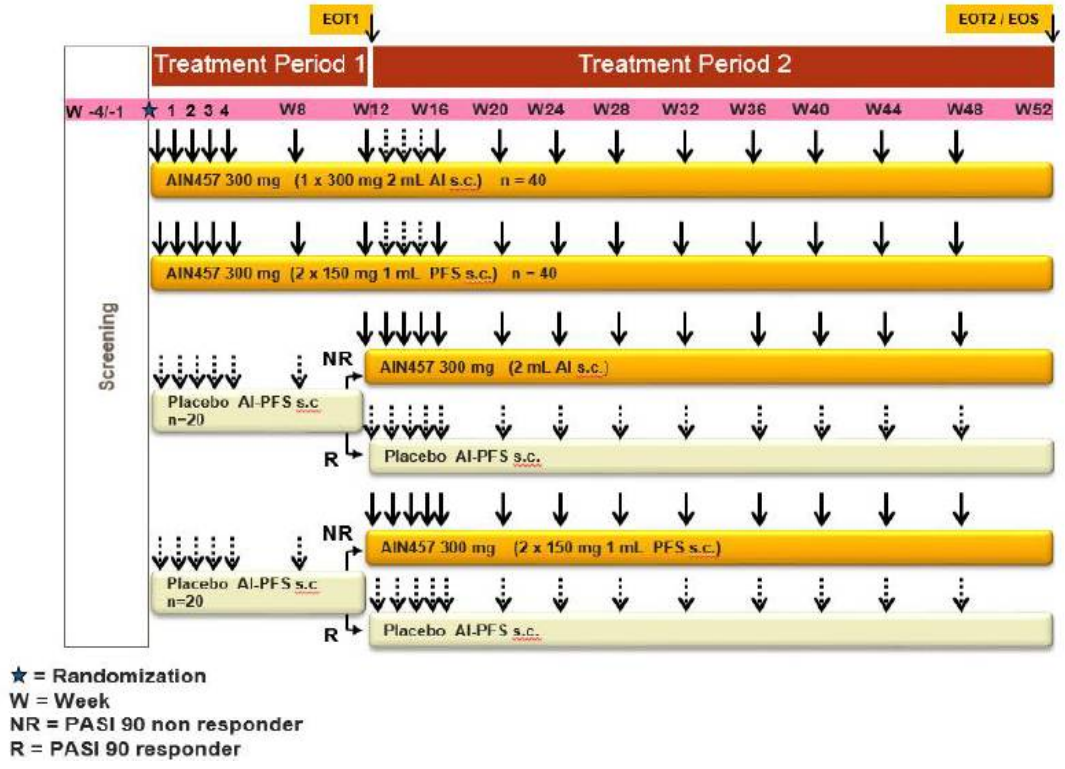
The following study periods will be considered for analysis:

- **Screening period** (before Randomization)
- **Treatment period 1** (Randomization to Week 12 pre-dose)
- **Treatment period 2** (Week 12 dose to Week 52)
- **Entire treatment period** (Randomization to Week 52, last dose at Week 48)

Of note, no follow-up period is included in this study.

The primary analysis will be provided at the time of Week 16 interim DBL. Treatment period up to Week 16 will be presented for the W16 primary analysis and all data will be presented for the final analysis. The study design is presented in Figure 3-1.

Figure 3-1 Study design



★ = Randomization
W = Week
NR = PASI 90 non responder
R = PASI 90 responder

In the figure, the solid arrow means active drug dosing while the dotted arrow means placebo dosing.

1.2 Study objectives and endpoints

The primary objective of this study is to demonstrate the efficacy of secukinumab 300 mg when administered in 2 mL auto-injector in subjects with plaque-type psoriasis with respect to both PASI 75 and IGA mod 2011 0 or 1 response (co-primary endpoint) at Week 12, compared to placebo.

The key secondary objectives is to demonstrate the efficacy of secukinumab 300 mg when administered in 2 mL AI in subjects with plaque-type psoriasis with respect to PASI 90 at week 12, compared to placebo.

Furthermore, additional aspects of efficacy, safety and tolerability of secukinumab 300 mg when administered with a 2 mL auto-injector in subjects with plaque-type psoriasis compared to placebo will be investigated. The subject usability and satisfaction with the new secukinumab 2 mL auto-injectors utilizing a self-administered Self-Injection Assessment Questionnaire (SIAQ) and investigator/site staff observation of secukinumab 300 mg 2 mL auto-injector administration will be assessed.

This study will provide efficacy and safety data to support a product labeling updates for the indication of moderate to severe plaque psoriasis.

Table 1-1 Primary, key secondary, secondary [redacted]

Variable	Type
PASI 75 response @ Week 12	primary
IGA 0/1 response @ Week 12	primary
PASI 90 response @ Week 12	key secondary
PASI 50/75/90/100 and IGA 0/1 response over time	secondary
PASI score and IGA mod 2011 categories over time	secondary
Device usability (Instructions For Use(IFU) and use-related hazards)	secondary
SIAQ	secondary
DLQI score	secondary
DLQI 0 or 1 achievement	secondary
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Novartis will be performing both Week 16 primary analysis and final analysis. Statistical software SAS version 9.4 or later will be used.

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

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

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

All listings will be presented by treatment sequence.

Footnotes on outputs will be kept to a minimum also for outputs not covered in MAP TLF shells.

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

2.1.1 General definitions

2.1.1.1 Study treatment

The following study drugs will be used:

- Investigational treatment
  - Secukinumab 300 mg, provided as one 2 mL auto-injector (AI)
- Control treatment
  - Secukinumab 300 mg, provided as two 1 mL pre-filled syringes (PFS) containing 150 mg secukinumab
  - Secukinumab placebo, provided as either one 2 mL AI or two 1 mL PFS

2.1.1.2 Study Day 1 and other study days

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

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

The descriptor "Day 0" will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

Screening refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the date of first dose of study treatment (for safety analysis) or prior to the randomization date (for efficacy analysis). Per protocol, subject informed consent must be obtained prior to performing any study related activity. The date of signing informed consent is the start date of screening period. Any assessment obtained during the screening period will be labeled screening assessment. Assessments made on Day 1 may occur before or after the randomization or the first dose. Further information will be found in [Programming Datasets Specifications (PDS)].

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

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

Of note, baseline will be derived based on the randomization day or first dose day, exact randomization/dosing time is not considered.

Of note, re-randomization will not be used for baseline definition and only one baseline value will be defined referring to the first randomization.

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the CRF. Duration of exposure is defined in Section 2.4.1.

For safety analysis, on-treatment is defined as assessments within last dose plus 84 days.

Of note: study does not have follow up period, the last visit is 4 weeks after last dose.

2.2 Analysis sets

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

Randomized set: The randomized set will be defined as all subjects who were randomized at baseline visit. Unless otherwise specified, subjects with missing informed consent form as well as mis-randomized subjects will be excluded from the randomized set.

Misrandomized subjects are subjects who are screen-failures, but have been randomized by the investigator before eligibility was finally assessed, however have not been treated. If previously mis-randomized subjects were re-screened and successfully randomized, they will be included in the randomized set according to the treatment assigned in the last randomization.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization. If the actual randomization stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses. The subjects with severe GCP violation will not be included in the FAS.

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

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

2.2.1 Subgroup of interest

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

Table 2-1 Subgroup definitions

Subgroup variables	Categories	Label for outputs	Suffix for outputs*
Weight category	body weight category (<90 kg, >=90 kg)	Weight category	a

* Suffixes will be used for the outputs numbering, see [TFL shell document]

Table 2-2 Subgroup analyses

Endpoint/analysis	Weight category
Co-primary endpoints:	
PASI 75 response @ Week 12	X
IGA 0/1 response @ Week 12	X
Secondary endpoints:	
PASI 90 response @ Week 12	X
PASI 50/75/90/100 response over time up to week 52	X
IGA 0/1 response over time up to week 52	X

Note: presented are only those endpoints that need subgroup analyses.

2.3 Patient disposition, demographics and other baseline characteristics

The summaries will be shown for the following treatment groups,
before or at Week 12:

- AIN457 300 mg (2mL AI), AIN457 300 mg (2x1mL PFS), Placebo, Total

after Week 12:

- AIN457 300 mg (2mL AI), AIN457 300 mg (2x1mL PFS), Placebo, Placebo - AIN457 300 mg (2mL AI), Placebo - AIN457 300 mg (2x1mL PFS), Total

No summaries for entire treatment period will be provided.

The following common background and demographic variables will be analyzed:

Continuous variables:

- Age (which is collected in the RaveX platform directly)
- Height
- Weight
- Body mass index (BMI)

Categorical variables:

- Age categories (<65 years, 65 years and older, 75 years and older)
- Sex
- Race
- Ethnicity
- Smoking status at baseline
- Weight categories (<90 kg, >= 90 kg)

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

Continuous variables:

- Baseline PASI
- Baseline total BSA
- Time since diagnosis of psoriasis
- Time since diagnosis of psoriatic arthritis

Categorical variables:

- Baseline PASI categories (≤20, >20)
- Baseline IGA mod 2011 score categories (at least mild, moderate, severe)
- Severity of psoriasis categories (CHMP guidelines, mild (total BSA <10% and PASI < 10) , moderate ((PASI ≥10 or total BSA≥10%) and PASI ≤20 and total BSA ≤20%), severe (total BSA >20% or PASI > 20))
- Baseline psoriatic arthritis categories (yes, no)
- Previous exposure to biologic systemic psoriasis therapy (yes, no)
- Previous exposure to systemic psoriasis therapy (yes, no)

- Previous exposure to non-biologic systemic psoriasis therapy (yes, no)
- Previous failure to biologic systemic psoriasis therapy (yes, no)
- Previous failure to systemic psoriasis therapy (yes, no)
- Previous failure to non-biologic systemic psoriasis therapy (including phototherapy and photo- chemotherapy) (yes, no)

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

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

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

Of note: subject's height will not be remapped according to the analysis visit window.

Time since diagnosis of psoriasis (PsO) and time since diagnosis of psoriatic arthritis (PsA) will be calculated using the following formula:

$$\text{Time since diagnosis} = (\text{inform consent date} - \text{first diagnosis date} + 1)/365.25$$

The first diagnosis date of PsO or PsA will be imputed according to the imputation rules in Section 5.1.4.

Unless otherwise specified, summary statistics will be presented for continuous variables for each treatment group and for all subjects (total) in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total) in the randomized set.

Any condition entered on the *relevant medical history / current medical conditions* CRF (including family history) will be coded using the MedDRA dictionary. They will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA dictionary.

Summaries for cardiovascular medical history will be summarized by categories.

Smoking history will be summarized by treatment group.

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

2.3.1 Patient disposition

The number of subjects screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of subjects in the randomized set who completed study periods and who discontinued the study prematurely (including the reason for discontinuation) will be presented for each treatment group and all subjects.

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

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

The number of secukinumab 2mL auto injections, 1mL secukinumab syringe, secukinumab placebo injections will be summarized by treatment group by means of contingency tables.

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain time thresholds will be displayed. The following categories will be presented: “any exposure”, “≥1 week”, “≥2 week”, “≥3 week”, “≥4 weeks”, “≥8 week”, “≥12 weeks”, “≥16 weeks”, “≥28 weeks”, “≥40 weeks” and “≥52 weeks”.

Duration of exposure will be defined as the time from first dose of study medication to the last dose plus 84 days or last visit 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 or in the corresponding treatment period.

Duration of exposure (days) = min (“end of study period” date, last dose date +84) – first dose date +1

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

Duration of exposure (100 subject years) = duration of exposure (years) / 100

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

2.4.1.1 Visit window

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-3. In this table, the days are counted since the first dose of study treatment (Day 1) for safety assessments, and the days are counted since the date of randomization for efficacy assessments. These visit windows apply to measurements taken at every visit.

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 60 instead of on Day 29, it will be re-aligned to visit window *Week 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 2.4.1.2.

For parameters which are not collected at every visit (e.g., DLQI), visit windows will be combined. For example, if a parameter is measured at Week 12 and Week 28 only, Week 12 visit window will extend from Day 2 to Day 99 (combining Week 1 to Week 12 visit windows), and Week 28 will be extend from Day 100 to Day 239.

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.

Table 2-3 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
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 100-155
Week 28	28	197	Day 156-239
Week 40	40	281	Day 240-323
Week 52	52	365	Day 324-421

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments.

Of note: subject's height will not be remapped according to the analysis visit window.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window (after Day 421) it is not assigned an analysis visit and will be listed under label "After Week 52".

2.4.1.2 Multiple assessments within visit windows

When there are *multiple assessments* in a particular visit window, the following rules are applied to select one value "representing" the subject in summary statistics in a visit window (See Table 2-4).

For baseline assessment definition see Section 2.1.1.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. PASI 90 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-4 Rules for selecting values for analysis within a given visit window

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1.1.3.
Post-baseline efficacy	All data except for PRO, e.g., PASI, IGA	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same day then select the first one using eCRF visit number. If two measurements have been taken on the same day and same visit then select the worst.
Post-baseline efficacy	PRO data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements have been taken on the same day, select the worst. If two measurements have the same value, select the first one using eCRF visit number.
Post-baseline safety	Summary visit information (e.g. laboratory values, vital signs, etc.)	The (non-missing) measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. If two measurements are taken on the same day then select the first one (using the time). If two measurements are taken on the same date/time then use the first eCRF visit number (assuming this is the planned visit).If two measurements are taken on the same date/time/eCRF visit number then take the average value of these two results.
Post-baseline safety	Notable abnormalities (e.g. vitals signs) and CTCAE grades for laboratory values	The most extreme measurement in the window will be used. Note this means a subject can have a notably high and notably low measurement within an analysis period.

2.4.2 Prior, concomitant and post therapies

Medications will be identified using Novartis Drug and Therapy Dictionary (NovDTD) including Anatomical Therapeutic Chemical (ATC) code. Prior and concomitant treatments will be summarized by treatment group for the safety set unless otherwise specified. Concomitant treatments will be displayed for the treatment period 1 and entire treatment period.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Prior medications are defined as drugs taken and stopped prior to the first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment, and last dose plus 84 days or last visit whichever occurs earlier will be a **concomitant** medication, including those which were started pre-baseline and continued into the treatment period.

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

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

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

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

2.5.1.1 Definition of PASI and related variables

The investigator or trained qualified designee will complete the PASI assessments. Whenever possible, the same evaluator should perform this assessment at all visits.

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs (see below for PASI assessment). The following calculations will be done: each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting 4 percentages will be added up to estimate the total BSA affected by plaque-type psoriasis. The PASI scoring system is further described in Table 2-6.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 2-6. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

1. The neck is assessed as part of the head.
2. The axillae and groin are assessed as part of the trunk.
3. The buttocks are assessed as part of the lower limbs.

4. When scoring the severity of erythema, scales should not be removed.

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

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

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively (see Table 2-6).

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

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

Table 2-5 The PASI scoring system

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

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

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

- **PASI 50 response**: subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders
- **PASI 75 response**: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response**: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response / remission**: complete clearing of psoriasis (PASI=0)

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

The IGA mod 2011 rating scale for overall psoriatic disease (shown in Table 2-6) has been developed based on a previous version of the scale used in secukinumab phase II studies, and has been updated in collaboration with health authorities (in particular the FDA). The explanations/descriptions of the points on the scale have been improved to ensure appropriate differentiation between the points. It is recommended that the same evaluator conducts the assessments throughout the study whenever possible.

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

Table 2-6 The IGA mod 2011 rating scale

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

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

Subjects require an IGA mod 2011 score at randomization of 3 or 4 in order to participate in the study. Based on this scale, subjects will be considered as **IGA mod 2011 0 or 1 responder** if they achieve a score of 0 or 1 and improve by at least 2 points on the IGA mod 2011 scale compared to baseline.

2.5.1.3 Overview of analysis methods of efficacy variables

An overview of statistical analyses and methods applied to psoriasis efficacy variables is given in Table 2-7.

Table 2-7 Overview of analysis methods for efficacy variables

Variable(s)	Summary statistics for binary/ categorical data	Logistic regression	Summary statistics for continuous data	Time-to-event analysis	Graphs
PASI 75 response @ Week 12	X	X			X*
IGA 0/1 response @ Week 12	X	X			X*
PASI 90 response @ Week 12	X	X			X*
PASI 50/75/90/100 and IGA 0/1 response over time	X	X			X**

Variable(s)	Summary statistics for binary/ categorical data	Logistic regression	Summary statistics for continuous data	Time-to-event analysis	Graphs
PASI score over time			X		X**
IGA mod 2011 categories over time	X				
Device usability (IFU and use-related hazards)	X				
SIAQ			X		
DLQI score over time			X		
DLQI 0/1 over time	X				

* dot plot; ** time course plot

2.5.2 Statistical hypothesis, model, and method of analysis

The co-primary endpoints of this study are PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

The statistical hypothesis is that secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to the proportion of subjects with PASI 75 response and IGA mod 2011 0 or 1 response at Week 12.

Let p_j denote the proportion of PASI 75 responders at Week 12 for treatment group j and r_j denote the proportion of IGA mod 2011 0 or 1 responders at Week 12 for treatment group j, $j = 1, 0$ where,

- 0 corresponds to placebo
- 1 corresponds to secukinumab 300 mg (2 mL AI)

The following hypothesis will be tested:

- $H_1: p_1 - p_0 \leq 0$ versus $H_{A1}: p_1 - p_0 > 0$,
- $H_2: r_1 - r_0 \leq 0$ versus $H_{A2}: r_1 - r_0 > 0$

In other words:

H_1: Secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to PASI 75 response at Week 12

H_2: Secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to IGA mod 2011 0 or 1 response at Week 12

The primary analysis method will be the logistic regression with treatment group (secukinumab 2mL AI vs Placebo); baseline bodyweight strata and baseline PASI score as explanatory variables. Odds ratios will be computed for comparisons of secukinumab dose regimen versus placebo utilizing the logistic regression model fitted. In case of the logistic regression does not converge due to low reponse rates in the placebo group, an exact logistic regression with be performed and the detailed analysis is described in Section 4.2.3. In case of response rates of 0% or of 100% in one of the treatment groups, confidence intervals and p-values from the t-test for the risk difference comparing to 0 will be provided for the analyses using multiple imputation; for the analyses using non-responder imputation, Fisher's exact test will be performed and confidence intervals for risk difference will be provided.

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

1. Run the PROC GENMOD procedure with EXACT statement;
2. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with continuous covariates (baselines PASI score), followed by removing categorical covariates (i.e., weight stratum etc.,);
3. If convergence not reached, perform Fisher's exact test.

The hypotheses H_1 and H_2 will both be tested at level 2.5% (one-sided), and significant results will only be achieved if both tests are rejected. If only one hypothesis is rejected and the other hypothesis is not rejected, superiority of secukinumab 300 mg (2 mL AI) has not been demonstrated.

Summary statistics and figures will be provided as described in Section 5.4.2. Details in sensitivity analysis are provided in Section 2.5.4.

2.5.3 Handling of missing values/censoring/discontinuations

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

Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Within this analysis the PASI score or IGA mod 2011 categories will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

(Modified) Non-responder imputation will be used as a sensitivity method: Missing values with respect to response variables based on PASI score and IGA 2011 categories will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues), exceptions will apply to the following:

- If a subject dropped out of the study prior to last scheduled visit and being responder consecutively at least for two preceding visits, the subject will be imputed as responder after discontinuation and up to the last scheduled visit.
- If a subject who was responder at visit *x*-1 and visit *x*+1 but has missing data at visit x, then the subject will be imputed as responder for visit *x* as long as the distance between the scheduled visits *x*-1 and *x* is 4 weeks or less, and the distance between the scheduled visits *x* and *x*+1 is 4 weeks or less. Otherwise missing data will be imputed with non-response.

Some examples are illustrated below:

Visit	1	2	3	4	5	6	7	8	9	10
Pat										
A	*R*	*NR*	*R*	.	.	.	.	.	.	.
A imp				*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
B	*NR*	*R*	*R*	.	.	.	.	.	.	.
B imp				*R*	*R*	*R*	*R*	*R*	*R*	*R*
C	*R*	*NR*	*R*	.	.	*R*	*R*	.	*R*	*NR*
C imp				*NR*	*NR*			*R*		

Summary tables for PASI scores and IGA mod 2011 categories will be imputed using MI. The mean for PASI score and the number (%) for IGA mod 2011 categories as well as their 95% confidence intervals will be given. In addition, PASI scores and IGA mod 2011 categories based on LOCF imputation will be provided in summary tables and listings.

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

2.5.4 Supportive analyses

Sensitivity analyses will be performed as follows:

(A) Co-primary endpoints (PASI 75 and IGA 0 or 1 response at Week 12) and key secondary endpoints will be evaluated using the logistic regression as described in primary analysis method with non-responder imputations instead of multiple imputation for missing values.

2.6 Analysis of the key secondary objective

2.6.1 Key secondary endpoint

The key secondary endpoint of this study is PASI 90 response at Week 12.

2.6.2 Statistical hypothesis, model, and method of analysis

Testing strategy

As stated in Section 2.5.2, the hypotheses H_1 and H_2 will be included in co-primary testing procedure. Each hypotheses is tested at $\alpha = 2.5\%$ (one-sided). The testing sequence will continue to key secondary endpoint PASI 90 at $\alpha = 2.5\%$ (one-sided) only if both H_1 and H_2 have been rejected at α (one-sided) such that a family-wise type-I-error of α (one-sided) is kept.

H_3: secukinumab 300 mg (2 mL AI) is not superior to placebo with respect to PASI 90 response at Week 12

PASI 90 response will be analyzed analogously to the primary endpoints at Week 12, i.e., the logistic regression model with treatment group, baseline bodyweight strata and baseline PASI score as exploratory variables. Odds ratios will be computed for comparisons of secukinumab versus placebo utilizing the logistic regression model fitted.

2.6.3 Handling of missing values/censoring/discontinuations

See Section 2.5.3.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

PASI 50, PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response over time

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

For PASI 50, PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response at each visit, up to Week 12, comparisons between 2mL AI vs placebo and 2mL AI vs 1mL PFS x 2 will be conducted using logistic regression model with treatment group, body weight stratum and baseline PASI as effects.

For PASI 50, PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response, the placebo adjusted response rates (i.e., risk difference) including 95% confidence interval (based on normal approximation) will be derived by visit, up to Week 12. In addition, Fisher's exact test will be applied to the treatment group comparisons between 2mL AI versus placebo. In addition, the risk difference between 2ml AI group vs. 1ml PFS group, including 95% confidence interval (based on normal approximation) may be derived by visit, up to Week 52.

Figures will be provided as well displaying estimates for response rates over time by treatment including 95% confidence intervals.

PASI score over time

Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group. Figure will be provided for percentage changes in PASI scores over time.

IGA mod 2011 score over time

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

2.7.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.7.3 Handling of missing values/censoring/discontinuations

See Section 2.5.3.

2.8 Safety analyses

All safety analyses will be based on the safety set. Only those scheduled visits which were pre-planned in the protocol will be reported in tables and figures for safety variables.

Treatment groups for evaluation of entire treatment

The summaries of evaluation will be reported for treatment period 1 and entire treatment period, respectively. Week 16 primary analysis will include data up to Week 12 for treatment period 1 and data up to Week 16 last patient last visit (LPLV) for the entire treatment period.

The following groups will be used for treatment period 1:

- **AIN457 300 mg (2mL AI)**: all subjects who are randomized to 300 mg 2mL AI group at Randomization visit
- **AIN457 300 mg (2x1mL PFS)**: all subjects who are randomized to 300 mg 2x1mL PFS group at Randomization visit
- **Placebo**: all subjects who are randomized to a placebo group at Randomization visit
- **Any AIN457 300 mg**: Any AIN457 300 mg of (2mL AI) or (2x1mL PFS) as above.

The following groups will be used for entire treatment period:

- **AIN457 300 mg (2mL AI)**: all subjects who are randomized to 300 mg 2mL AI group at Randomization visit
- **AIN457 300 mg (2x1mL PFS)**: all subjects who are randomized to 300 mg 2x1mL PFS group at Randomization visit
- **Any AIN457 300 mg (2mL AI)**: all subjects who are randomized to 300 mg 2mL AI group at Randomization visit and all placebo subjects who are re-assigned to 300 mg 2mL AI at Week 12, but they are only considered after the treatment re-assignment (Week 12 treatment injection).
- **Any AIN457 300 mg (2x1mL PFS)**: all subjects who are randomized to 300 mg 2x1mL PFS group at Randomization visit and all placebo subjects who are re-assigned to 300 mg 2x1mL PFS at Week 12, but they are only considered after the treatment re-assignment (Week 12 treatment injection).
- **Any AIN457 300 mg**: Any AIN457 300 mg of (2mL AI) or (2x1mL PFS) as above.
- **Placebo**: all subjects who are re-assigned will only be considered until the re-assignment point (Week 12 treatment injection).

2.8.1 Adverse events (AEs)

For adverse events and other binary safety variables crude incidence and exposure time-adjusted incidence will be derived as described below and summarized in Table 2-8.

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

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

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

Table 2-8 Overview of analyses on some safety endpoints

Analysis period	AEs & SPP/RMP risks	SAEs	AEs-SMQ	AEs by severity	study treatment related AEs, death & other significant AEs	notables (lab/vitals)
treatment period 1 (up to week 12)	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire treatment period (including all data)	• crude incidence • exp.time adjusted incidence*	• crude incidence • exp.time adjusted incidence*	• crude incidence • exp.time adjusted incidence*	• crude incidence	• crude incidence	• crude incidence

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

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

The crude incidence of treatment emergent adverse events will be presented for the treatment period up to Week 16 LPLV for W16 primary analysis, and treatment period including all data for final analysis. The crude incidence of treatment emergent adverse events will be summarized by primary System Organ Class (SOC) and Preferred Term (PT). Confidence intervals for the crude rate will be derived using the score method including continuity correction (Newcombe 1998) as described in Section 5.4.5. In addition, exposure time-adjusted incidence rates will be provided for the treatment period including all data (see Section 5.4.6).

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

Adverse events will also be reported separately by standardized or customized MedDRA queries (SMQ or CMQ/NMQ).The MedDRA version used for reporting the adverse events will be described in a footnote.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT or ≥ z % in any group for each grouping term table) will be presented in descending frequency according to its incidence in secukinumab group starting from the most common event. Here threshold value z is set to 2 (%) but it may be updated following review of the dry run outputs.

A graphical display of the crude rates or exposure adjusted incidence rates within system organ classes will be presented as follows: For all AEs regardless of severity and seriousness, the point estimate within system organ classes will be presented graphically with system organ class on the y-axis. This figure will consist of two panels: i) point estimate of AEs, ii) point estimate of serious AEs. For the exposure adjusted incidences a linear-scale will be used on the x-axes.Separate summaries will be provided for deaths, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment or interruption.

Algorithms for date imputations will be provided in Section 5.

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

Crude rate of important identified and potential risks from Case Retrieval Sheet will be provided for all (non-serious and serious) cases and for all serious cases. Exposure-time adjusted rates will be provided for treatment period including all data for all (non-serious and serious) cases and for all serious cases. In addition, listings will be provided for the related AE risks.

Risk measures and confidence intervals will be derived according to Section 5.

The version of the Case Retrieval Sheet used for the analyses will be described in a footnote. This includes MedDRA version and Novartis MedDRA Query (NMQ) dictionary date.

A separate table of injection site reaction related AEs caused by the 2 mL AI and the 1 mL PFS respectively will be provided. Additional analyses on the severity, outcome, etc. of the AEs caused by AI and PFS respectively may be performed to support health authority interactions as necessary.

Important note: For the evaluation of risks primary and secondary system organ classes of the MedDRA dictionary will be considered.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on adverse events which are not serious adverse events (PT) with an incidence greater than >2% and on SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

Separate summary and listing will be provided for deaths.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry).

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

change from baseline = post baseline value – baseline value

Only "on-treatment" laboratory data will be summarized (i.e. assessments within last dose plus 84 days). All laboratory data will be listed with "on-treatment" flag displayed. If two measurements are taken on the same date/time/CRF visit then use the average of two assessments.

For laboratory test values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ value, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")." For example, the actual lab result is "<5" and LLQ = 10, it will be reported for the numerical part as 5 and listed as "<5", LLQ will be imputed as 5.

In addition, shift tables may be provided as required at ad-hoc basis for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within a treatment period. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high (including category "high and low"). These summaries will be presented by laboratory test and treatment group. Subjects with abnormal laboratory values will be listed and values outside the normal ranges will be flagged.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2-9: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP).

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

Table 2-9 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 – 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) during the treatment phase analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase. If no pre-treatment value exists, also a value recorded after first dose can be used as baseline if it was collected on the same day as first dose, see Section 2.1.1.3.

Exposure time adjusted incidence for subjects with newly occurring neutropenia of CTCAE grade >=2 will be summarized

The number and percentage of subjects with newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-10.

Table 2-10 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 ALT or AST >3xULN & (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))
TBL	>1xULN;>1.5xULN; >2xULN; >3xULN,
ALP	>1.5xULN;>2xULN; >3xULN; >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >1.5xULN; ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN; ALT or AST >20xULN & TBL >2xULN;
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN
ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of *pure hepatocellular injury*. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI. ALT or AST>3xULN & TBL >2xULN & ALP <2xULN **(Potential Hy's Law**) or reported Hy's Law case Note: "Hy's Law case" is a lower level term in MedDRA (10070546) and may be reported as AE.

For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same visit. The criteria are not mutually exclusive, e.g., a subject with ALT = 6.42xULN is counted for ALT >3xULN and ALT>5xULN.

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

Fasting laboratory tests including fasting plasma glucose and fasting lipids will be evaluated only at screening. No analysis will be done for these measurements.

For urinalysis, standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood (non-hemolyzed), urine blood (hemolyzed), bilirubin, ketones, WBC will be done at screening. No analysis will be done for these measurements.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

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

2.8.4.2 Vital signs

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

change from baseline = post-baseline value – baseline value

Only "on-treatment" vital signs will be summarized (i.e. assessments within last dose plus 84 days). All vital signs will be listed with "on-treatment" flag displayed.

The number and percentage of subjects with newly occurring notable vital signs abnormalities will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-11 below. A listing of subjects with newly occurring notably abnormal vital signs will be provided.

Table 2-11 Criteria for notable vital sign abnormalities

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

[redacted]

2.11 Clinician-reported outcomes

2.11.1 Usability and hazard assessment of the 2 mL auto-injector

This analysis will be based on the Safety Set.

The number and percentage of subjects who successfully completed each and ALL of the indicated steps as per the IFU will be summarized by visit and treatment group, including total.

The number and percentage of subjects who experienced each and ANY of the defined possible hazards will be summarized by visit and treatment group, including total.

Successful self-injection will be positively defined for a subject when the subject performs the six critical steps as per the IFU (i.e. P7, P9, P10 and P11). Number and percentage of subjects who passed the self-injection successfully as well as a two-sided 95% exact confidence interval at Week 1 visit will be summarized by visit and treatment group, including total. The following statistical hypothesis will be tested by an exact binomial test at one-sided 2.5% level of significance at Week 1 visit:

H_0: successful auto-injector use rate $< 90\%$

H_1: successful auto-injector use rate $\geq 90\%$

Missing values with respect to the self-assessment checklist and possible hazard assessment checklist will not be imputed while summarizing the answers of each question with frequencies.

Subjects with one or more of the critical steps missing will be considered as unsuccessful (imputation with non-response) with regard to the self-injection success. Subjects who discontinued or who missed a visit and have the full self-injection checklist missing will not be evaluated with regard to the self-injection success at the corresponding visit.

Visit windows will not be applied to self-injection assessment and possible hazard assessment. The analysis visit will refer to the visit as per the CRF.

Of note: only data in the self-assessment checklist with self-injection checked in eCRF Dosage Administration Record (DAR) page are included in the analyses.

2.12 Patient-reported outcomes

Summaries will be based on the FAS and will be presented separately for each treatment group.

For DLQI, missing values will be replaced by LOCF. Baseline values will not be carried forward. If no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose. In addition, missing baseline (PROs) values will be replaced by the means or modes of non-missing baseline values stratified by age group (<65 years, 65 years and older) and sex, for continuous scale or categorical/ordinal scale, respectively.

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”. “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.

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

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1. Treatment groups will be compared by Fisher’s exact test.

Self-Injection Assessment Questionnaire (SIAQ)

All SIAQ analyses will be based on the Safety Set.

Summary statistics for the absolute values of the domain scores at Randomization (baseline) will be provided by treatment group including total for the PRE-module and the POST-module. The number and percentage of subjects in each of the 5 categories (likert scale) for each item will be presented by visit and treatment group including total.

Item and domain scores from the PRE module taken before the first self-injection at Randomization (baseline) will be compared with the corresponding item and domain scores (feeling about injections, self-confidence domains, and overall satisfaction of self-injection item) from the POST modules. Change in domain scores from PRE module will be summarized by visit and treatment group including total.

Domain scores will be calculated only if 50% or more items of the domain are completed. Missing items will not be imputed. Subjects who discontinued or who missed a visit and have the SIAQ questionnaire not completed will not be considered in the analyses at the corresponding visit.

2.13 Biomarkers

Not applicable.

[redacted]

2.15 Interim analysis

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

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

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

Trial modifications are not planned based on any interim analysis.

3 Sample size calculation

A response rate of 8% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group is expected, whereas a response rate of 62% for PASI 75 response and 55% for IGA mod 2011 0 or 1 is the anticipated response in the secukinumab 300 mg 2 mL auto-injector s.c.group.

Placebo-response rates between 3% and 7% have been reported in Papp et al 2005, Menter et al 2008, Leonardi et al 2008, and Papp et al 2008.

3.1 Primary endpoint (co-primary endpoint)

With respect to the co-primary endpoint (PASI 75 response and IGA mod 2011 0 or 1 response at Week 12), the type-I-error will be 2.5% one-sided for comparison. With 40 subjects per group and assuming a response rate of 8% for PASI 75 response and IGA mod 2011 0 or 1 response in the placebo group, the power to show a response rate of 62% for PASI 75 response and 55% for IGA mod 2011 0 or 1 response in the secukinumab 300 mg (2 mL auto-injector s.c.) group based on Fisher's exact test (nQuery Advisor 7.01, two group Fisher's-exact test of equal proportions) is above 99% for PASI 75 response and IGA mod 2011 0 or 1 response.

3.1.1 Secondary endpoints

The study should be sufficiently powered (above 90%) to show a response rate of 46% for PASI 90 response if the placebo rate is assumed as 8%.

4 Change to protocol specified analyses

The following analyses have been removed:

- The maximum change (maximum decrease and maximum increase) from baseline within treatment period for each laboratory parameter
- The stratified Van-Eltern testing and Hodges-Lehmann estimates for the absolute value and the percentage change from baseline of DLQI total score.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

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

5.1.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), 31DECYYYY, date of death).

2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death).

3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).

2. Else AE start reference date = treatment start date

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

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

a. If AE 'month' is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE 'month' is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

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

a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

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

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

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date and the last day of the month.

2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).

3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:

a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

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

a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).

b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:

a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.

b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).

c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.4 First diagnosis date (PsO, PsA) imputation

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

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

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

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

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

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

5.1.5 Other imputations

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

For DLQIscore, missing values will be replaced by LOCF. Baseline values will not be carried forward. If no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose. In addition, missing baseline values will be replaced by the means or modes of non-missing baseline values stratified by age group (<65 years, 65 years and older) and sex, for continuous scale or categorical/ordinal scale, respectively.

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

5.2 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote.

Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the

Program Case Retrieval Sheet that is stored in [redacted]

5.3 Laboratory parameters derivations

See Section 2.8.3.

5.4 Statistical models

5.4.1 Analysis of continuous data

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

5.4.2 Analysis of binary (and categorical) data

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. If applicable, confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With $_z$ as (1-alpha/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), $_n$ as total number of subjects (i.e. number of subjects in the denominator), and $p$as estimated crude incidence (number of subjects with event / $_n$) it is $q = 1 - p$

Then the lower limit is for $p > 0, \left(L = 0 \text{ for } p = 0\right),$

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

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

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

For response variables (e.g. for IGA mod 2011 0 or 1, PASI 75, PASI 50, PASI 90 and PASI 100 response) the placebo adjusted response rates (risk difference) including 95% confidence interval will be derived by visit.

Figures will be provided for PASI 75 response (upper left) PASI 90 response (upper right), PASI 100 response (lower left) and IGA mod 2011 0 or 1 response (lower right) at Week 12 as dot plots displaying treatments on the x-axis and point estimates including 95% confidence intervals on the y-axis.

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

5.4.3 Logistic regression

Binary outcome variables, including PASI 50 / 75 / 90 / 100 response and IGA mod 2011 0 or 1 response, will be evaluated using a logistic regression model with treatment regimen, baseline bodyweight strata and baseline PASI score. Odds ratios will be computed for comparisons of secukinumab dose regimen versus placebo utilizing the logistic regression model fitted.

If response rates are 0% or 100% in one of the treatment groups, Fisher's exact test will be applied. Confidence intervals for risk difference will be derived based on the exact method. Odds ratio estimate and p-values will not be displayed in outputs, but "-" will be shown.

The odds ratio will be calculated such that an odds ratio >1 is favorable for secukinumab. Using PROC GENMOD to calculate the confidence interval for the odds ratios assumes asymptotic normality of the Wald estimate for the regression coefficient. The 95% confidence interval for the regression parameter of the active treatment effect relative to control(s) will be calculated using an exponential transformation to create the confidence interval for the odds ratio.

All p-values reported on linear hypotheses about regression coefficients will be based on the Wald tests from Type III analyses. In the SAS procedure PROC GENMOD, a Type III analysis will be performed by adding the model options: TYPE3, DIST=BIN, and LINK=LOGIT.

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

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

4. Run the PROC GENMOD procedure with EXACT statement;
5. If convergence not reached, remove the covariates from the model one by one until convergence is reached; start with continuous covariates (i.e., baseline bodyweight by replacing with body weight stratum, and then baseline PASI score, followed by removing categorical covariates(i.e., weight stratum);
6. If convergence not reached, perform Fisher's exact test.

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

5.4.4 Multiple imputations for response variables

Primary and secondary endpoints will be evaluated by Logistic regression and odds ratio estimate as described in the primary analysis method with multiple imputations for missing values. In addition, logistic regression analysis for PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0 or 1 response by visits will be analyzed using multiple imputation method.

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

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

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

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

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100, and IGA mod 2011 0 or 1 response by visit will be presented in contingency tables with multiple imputations method.

The number of imputations will be set to 100, the seed for the random function will be set to 4572325 for this study. To generate the multiple imputed data sets, the SAS procedure MI can be used as follows:

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

```
ODS LISTING CLOSE;
ODS OUTPUT MissPattern=msgpat VarianceInfo=varinfo ParameterEstimates=param;
PROC MI DATA=<pasi_iga> OUT=<impdata> SEED=457<studycode> NIMPUTE=100;
 VAR <baseline weight> <failure to at least one biologic>
     <number of previous systemic therapies>
     <baseline PASI> <baseline IGA>
     <change from baseline PASI week 1> - <change from baseline PASI week primary endpoint>
     <IGA week1> - <IGA week primary endpoint>;
  BY <treatment group>;
RUN;
ODS LISTING;
```

Programming notes:

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

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

```
DATA <impdata2>;
 SET <impdata>;
IF <change from baseline PASI week primary endpoint>/<baseline PASI>=0.75 THEN <PASI 75 response> =1;
```

```
ELSE <PASI 75 response>=0;
<…repeat for all PASI response…>

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

The treatment differences for each imputed data set will then be evaluated by Logistic regression and ODDS ratio as described in Section 5.4.6.2. This analysis will be done by _IMPUTATION_ for the comparison to the placebo treatment group. The model should be estimating response probability = 1 by using DESECENDING option. Using the ESTIMATE option in the GENMOD procedure and the ODS OUTPUT data set "Estimates" provides the estimate for the odds ratio and confidence intervals.

```
PROC GENMOD <option>;
CLASS <stratum> <treatment>;
MODEL <response> = <explanatory variables> / link=logit dist=bin type3;
BY <by-variables);
ESTIMATE "OR. AIN 300 mg 2mL PFS VS. Placebo" <treatment> 1 0 -1/exp;
ESTIMATE "OR. AIN 300 mg 2x1mL PFS VS. Placebo" <treatment> 0 1 -1/exp;
ODS OUTPUT Estimates=Estimates;
RUN;
```

The MIANALYZE procedure expects the parameter estimate in the variables ESTIMATE, and the corresponding standard error in the variable STDERR. Measurements can be obtained from "Estimates" dataset by selecting the row with ODDS ratio estimates.

```
Data <modified dataset>;
  set Estimates;
  if substr(label,1,3)= "Exp";
  ESTIMATE=LBetaEstimate;
  STDERR=StdErr;
  effect= "OR";
  if missing(ESTIMATE) or missing(STDERR) then delete;
RUN;
```

The estimates and standard errors based on the 100 imputed data are then combined by applying Rubin's rules for multiple imputed data sets, see Little and Rubin (2002).

Programming notes:

- The variables ESTIMATE and STDERR in the input data set for the MIANALYZE procedure may not be missing. Records with missing values need to be deleted and the variable _IMPUTATION_ needs to be renumbered and regenerated since for each by-group the procedure expects consecutive numbers starting at 1.

- The ESTIMATE and STDERR in terms of odds ratios from logistic regressions will be transformed to follow a normal distribution before MIANALYZE procedure. They will be transformed back to Odds Ratio to get the corrected ESTIMATE and corresponding CIs.

The SAS procedure MIANALYZE will be applied as follows:

```
DATA <modified dataset_t>;
     SET <modified dataset>;
     estimate=log(ESTIMATE);
     stderr=(log(LBETAUPPERCL)-log(LBETALOWERCL))/(2*1.96);
RUN ;

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

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

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

```
ODS LISTING CLOSE;
PROC FREQ DATA=<Imputed dataset> ORDER=DATA;
     TABLES <treatment group>*<response variable>/riskdiff alpha=0.05;
     BY <By-variables>;
     ODS OUTPUT RiskDiffCol1=RiskDiffCol1;
RUN;
ODS LISTING;
DATA DRISK; SET RiskDiffCol1;
     WHERE control= “1” ;
     ESTIMATE=risk;
     STDERR=ase;
     effect=”Riskdiff”;
     IF missing(ESTIMATE) OR missing(STDERR) THEN DELETE;
RUN;
PROC SORT DATA=DRISK; BY <By-variables>; RUN;
ODS LISTING CLOSE;
ODS OUTPUT ParameterEstimates=results VarianceInfo=varinfo ModelInfo=Modelinfo;
PROC MIANALYZE PARAMS=drisk;
     by <By-variables>;
     modeleffects Riskdiff;
     stderr ase;
RUN;
```

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

5.4.5 Crude incidence and related risk estimates

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

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

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

With z as (1-α/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1 - p$.

Then the lower limit is

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

and the upper limit is

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

Note: if p = 0 then L = 0 and if p = 1 then U = 1.

If appropriate, an exact 100*(1-α)% confidence interval (Clopper-Pearson 1934) will be obtained by using the SAS procedure PROC FREQ with the EXACT BINOMIAL statement. However, the confidence interval derived via the score method including continuity correction will be the default in safety analyses.

5.4.5.2 Relative risk and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g., placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the relative risk is estimated as p_1/p_0 with $p_1=x_1/n_1$ and $p_0=x_0/n_0$.

An asymptotic 100*(1-α)% confidence interval on the relative risk will be based on the back-transformed large sample confidence limits on the log-transformed relative risk estimate which are obtained by application of the delta-method and Slutzky's theorem (Lachin 2000). The SAS procedure PROC FREQ with option RELRISK in the TABLES statement will be used to provide the asymptotic 100*(1-α)% confidence interval on the relative risk. The estimate is not computed if either x_1 or x_0 equals 0. In this case, or if the crude incidences are low in both groups, the relative risk will be approximated by the odds ratio for which an exact confidence interval will be obtained as specified in Section 5.4.6.3. If the relative risk is not well approximated by the odds ratio but asymptotic normality is questionable, STATXACT will be used.

5.4.5.3 Odds ratio and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g. placebo) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ with $p_1= x_1/n_1$ and $p_0=x_0/n_0$. A conditional exact 100*(1-α)% confidence interval will be obtained by using the SAS procedure PROC FREQ with statement EXACT OR.

5.4.5.4 Risk difference and 100*(1-α)% confidence interval

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g., placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event, the risk difference is estimated as p_1-p_0 with $p_1= x_1/n_1$ and $p_0=x_0/n_0$.

Exact unconditional confidence limits for the risk difference will be obtained with SAS procedure PROC FREQ and option RISKDIFF in the TABLES statement, specifying the RISKDIFF option also in the EXACT statement.

5.4.6 Exposure adjusted incidence rate and related risk estimates

5.4.6.1 Exposure adjusted incidence rate and 100*(1-α)% confidence interval

It will be assumed that for each of n subjects in a clinical trial the time t_j (j=1,...,n) to the first occurrence of a certain treatment emergent event is observed, or if the event was not experienced, the (censored) time to the end of the observation period or last dose plus 84 days whichever occur earlier. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event.

Conditionally on T, an exact 100*(1-α)% confidence interval for a Poisson variable with parameter θT and observed value D can be obtained based on (Garwood, 1936), from which an exact 100*(1-α)% confidence interval for D/T will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

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

5.4.6.2 Exposure-adjusted event rate and 100*(1-α)% confidence interval

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

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

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

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

5.5 Rule of exclusion criteria of analysis sets

Protocol deviations for exclusion from analysis sets are defined in Table 5-1.

Table 5-1 Subject classification rules

Analysis set	PD Categories Codes that cause subject to be excluded	Non-PD criteria that cause a subject to be excluded
Randomization set	NA	Misrandomized subject
FAS (Full Analysis Set)	DVSPID:INCL01, OTH17; OTH12	Misrandomized subject
Safety	DVSPID: INCL01, OTH17; OTH12	Subjects who did not take any study treatment

OTH17: Patient was rescreened, or new/updated ICF available but patient did not sign a new ICF

OTH12: Severe ICH-GCP non-compliance of study site

5.6 Clinician reported outcomes

5.6.1 Usability and hazard assessment of the 2 mL auto-injector

The goal is to measure and evaluate the usability of the auto-injector during observed use. During the first 2mL self-injection at the respective visits (Randomization and Week 1), site staff will observe and complete the self-injection assessment checklist (Table 5-2) to assess the ability to follow the instructions for use (IFU). The possible hazard checklist (Table 5-3) will be assessed for the 2mL self-injection at each of the two visits.

Primary usability assessment:

- Assessment of successful self-administration by the subject at Week 1. Successful self-injection is achieved when the subject performs all required steps effectively and safely to deliver the correct dose from the device at the correct injection site. The sequence of user steps (as per IFU) that are minimally required are P7, P9, P10 and P11 (Table 5-2), these 6 critical steps will be used to define successful administration. The general passing usability goal for 'successful use' task completion will be defined as ≥ 90% pass rate following these steps.

Secondary usability assessment:

- Assessment of subject use errors that occur during the First Use at Randomization (after initial training) and repeated self-injection at Week 1 (without retraining).
- Assessment of successful First Use by subject after initial training (at Randomization), for subjects who successfully perform the self-injection as defined above for the primary usability assessment (i.e. P7, P9, P10 and P11).

Table 5-2 Self injection assessment checklist (auto-injector)

No.	IFU indicated steps	Required to be completed for successful administration
P1	Washed hands with soap and water	No
P2	Cleaned the injection site	No
P3	Removed the auto-injector from the outer box	No
P4	Checked expiration date on auto-injector label	No
P5	Inspected the auto-injector for damage	No
P6	Inspected liquid for brown discoloration or particles	No
P7	Removed cap from auto-injector	Yes
P8	Discarded cap	No
P9	Hold the auto-injector at correct angle to the injection site	Yes
P10	Press the auto-injector firmly against the skin to trigger the injection (1st Click), and keep holding the auto-injector firmly against the skin	Yes
P11	Wait until the injection is complete, confirmed by the 2nd "click" and/or a check that the yellow indicator fills the window	Yes

No.	IFU indicated steps	Required to be completed for successful administration
P12	The auto-injector can now be removed	No
P13	Check again that the yellow indicator fills the window	No
P14	Disposed used auto-injector in a sharps container	No

Table 5-3 Possible hazard assessment checklist

No.	Possible hazard assessment checklist
H1	Was there a needle stick in a critical area (e.g. eye, carotid artery)?
H2	Was there a needle stick in a non-critical area?[1]
H3	Was any part of the device swallowed? If yes, please specify.
H4	Was an immediate-type allergic reaction noticed to device material?
H5	Was increased pain noticed by the patient due to a bent needle?
H6	Was the breakage of the device observed?[2]
H7	Was swallowing of material debris observed?
H8	Was any other problem observed?[3]
H9	Was less than the full dose administered?[4]

The following potential hazards from the Hazards Identified List ([AIN457_HID_Delta225-01]) have not been included as not being observable during self-injection observation: microbiological contamination, wrong drug, transfer of transmissible diseases.

[1] Excluding the actual injection into the appropriate injection site of the body

[2] If yes, then it is to be specified under which circumstances breakage occurred and which parts were affected, as well any additional problems (e.g. injuries) due to the breakage are to be described.

[3] If yes, then it is to be specified. Possible events might include: irritated skin; drug too cold when injected; the drug or device upon visual inspection appeared unsuitable for injection; intradermal instead of subcutaneous injection; and other events.

[4] If yes, then it is to be specified why, e.g. leakage from injection site, early removal.

5.7 Patient reported outcomes

The impact of psoriasis on various aspects of subjects' health-related quality of life will be assessed by the DLQI in this trial.

5.7.1 Dermatology Life Quality Index (DLQI)

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

The scoring of each question is as follows:

- Very much: Scored 3
- A lot: Scored 2
- A little: Scored 1

- Not at all: Scored 0
- Not relevant: Scored 0
- Question unanswered: Scored 0
- Question 7: "prevented work or studying": Scored 3

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

Meaning of DLQI Scores:

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

The DLQI will be analyzed under six headings as follows:

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

Interpretation of incorrectly completed questionnaires:

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

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

Handling of missing values:

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

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

5.7.2 Self-injection Assessment Questionnaire (SIAQ)

The Self-Injection Assessment Questionnaire (SIAQ) is a questionnaire to measure overall subject experience with subcutaneous self-injection, and to investigate its psychometric properties. The SIAQ is composed of two modules: the PRE-module and the POST-module. The PRE-module, which is completed at Randomization before the first self-injection (baseline), includes 7 items grouped into three domains: feelings about injections, self-confidence and satisfaction with self-injection. The POST-module, which is completed following the 2 mL AI and before the 1 mL PFS self-injections, includes several items addressing five principal domains: feelings about injections, self-confidence, injection-site reactions, ease of use, satisfaction plus a single item assessing self-image. Subjects will rate each item of the SIAQ on a 5-point semantic Likert-type scale ranging from 1 (worst experience) to 5 (best experience). Item score will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience). The domain score will then be calculated as the mean of the item scores included in the domain.

Respondent rates each item of the PRE SIAQ and items 1-9 and 15-21 of the POST SIAQ on a 5-point semantic Likert-type scale, and items 10-14 of the POST SIAQ on a 6-point semantic Likert-type scale. For all items, a score of 1 corresponds to the subject's worst experience and a score of 5 or 6 corresponds to the subject's best experience.

The scoring of domains is performed in 2 steps:

1. The raw item scores ranging from 1 to 5 are transformed into scores ranging from 0 (worst experience) to 10 (best experience).
2. The transformed scores for items contributing to a domain are then averaged into a domain score (Table 5-4).

Table 5-4 Scoring of domains from raw item scores

	Items	Transformed item score	Domain score calculation	Domain score range
PRE-module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
CO	4-6	((raw score)-1)*2.5		
SA	7	((raw score)-1)*2.5		

POST- module domain				
FL	1-3	((raw score)-1)*2.5	Average of transformed item scores	0-10
IM	4	((raw score)-1)*2.5		
CO	5-7	((raw score)-1)*2.5		
RE	8-9	((raw score)-1)*2.5		
EU	10-14	((raw score)-1)*2		
SA	15-21	((raw score)-1)*2.5		

FL=Feeling about injection, IM=Self-Image, CO=Self-Confidence, RE=Pain and skin reaction during or after the injection, EU=Ease of use of the self-injection device, SA=Satisfaction with Self-injection

PRE-module:

Item 1= In general, how afraid are you of needles?;
Item 2= In general, how afraid are you of having an injection?;
Item 3= How anxious do you feel about giving yourself an injection?;
Item 4= How confident are you about giving yourself an injection in the right way?;
Item 5= How confident are you about giving yourself an injection in a clean and sterile way?;
Item 6= How confident are you about giving yourself an injection safely?;
Item 7= Overall, how satisfied are you with your current way of taking your medication (self-injection)?

POST-module:

Item 1= In general, how afraid are you of needles?;
Item 2= In general, how afraid are you of having an injection?;
Item 3= How anxious do you feel about giving yourself an injection?;
Item 4= How embarrassed would you feel if someone saw you with the self-injection device?;
Item 5= How confident are you about giving yourself an injection in the right way?;
Item 6= How confident are you about giving yourself an injection in a clean and sterile way?;
Item 7= How confident are you about giving yourself an injection safely?;
Item 8a= During and/or after the injection, how bothered were you by: pain";
Item 8b= During and/or after the injection, how bothered were you by: burning sensation";
Item 8c= During and/or after the injection, how bothered were you by: cold sensation";
Item 9a= During and/or after the injection, how bothered were you by: itching at the injection site?";
Item 9b= During and/or after the injection, how bothered were you by: redness at the injection site?";
Item 9c= During and/or after the injection, how bothered were you by: swelling at the injection site?";
Item 9d= During and/or after the injection, how bothered were you by: bruising at the injection site?";
Item 9e= During and/or after the injection, how bothered were you by: hardening at the injection site?";
Item 10= How difficult or easy was it to remove the cap?;
Item 11= How difficult or easy was it to depress the plunger or button on the device?;
Item 12= How difficult or easy was it to administer the injection without any help?;
Item 13= How difficult or easy was it to use the self-injection device?;
Item 14= How does the device fit in your hand?;
Item 15= How easy was it to give yourself an injection?;
Item 16= How satisfied are you with how often you give yourself an injection?;
Item 17= How satisfied are you with the time it takes to inject the medication?;
Item 18= Overall, how satisfied are you with your current way of taking your medication (self-injection)?;
Item 19= Overall, how convenient is the self-injection device?;
Item 20= After this study, would you choose to continue self-injecting your medication?;
Item 21= After this study, how confident would you be to give yourself injections at home?

6 Reference

Alberti KGMM, Eckel RH, Grundy SM, et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation; 120: 1640-1645.

Bishop YMM, Fienberg SE, Holland PW (1991) Discrete multivariate analysis. Cambridge MA, 11th ed. The MIT Press

Bretz F, Maurer W, Brannath W, Posch M (2009) A graphical approach to sequentially rejective multiple test procedures. Statistics in Medicine; 28: 586-604.

Clopper CJ, Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26; 404–413.

Committee for medicinal products for human use (CHMP), European Medicines Agency for the Evaluation of Medicines for Human Use. (2004) Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 corr document. London, UK.

Fredriksson T, Pettersson U (1978) Severe psoriasis—oral therapy with a new retinoid. Dermatologica; 157:238–44.

Garwood, F (1936). Fiducial limits for the Poisson distribution. Biometrika, 46; 441–453.

Gottlieb A, Griffiths CEM, Ho VC, et al (2005) Efficacy and tolerability of oral pimecrolimus in the treatment of moderate to severe chronic plaque type psoriasis: a double-blind, multicentre, randomized dose-finding trial. Br J Dermatol; 152:1219-27.

'Japan Specific Requirements from PMDA' guidance, available in [redacted]

Kenward, M. and Roger, J. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics; 53: 983-997.

Lachin JM (2000) The assessment of relative risks . New York: Wiley

Little, R.J.A and Rubin, D.B. (2002). Statistical Analysis with Missing Data. Wiley Series in Probabiliy and Statistics, Chapter 10.

Menter A, Gottlieb A, Feldman S, et al (2008) Guidelines of care for the management of psoriasis and psoriatic arthritis – Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol; 58:826-850.

Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.

Papp KA, Tyring S, Lahfa M et al (2005) A global phase II randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol; 152:1304-12.

Program Case Retrieval Sheet available in [redacted]

Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: Wiley.

[redacted]

Sahai H, Khurshid Anwer (1993). Confidence intervals for the mean of a poisson distribution: a review. Biom J, 35 (7); 857-867

Sampson HA, Muñoz-Furlong A, Bock SA, et al (2005) Symposium on the Definition and Management of Anaphylaxis: Summary report. J Allergy Clin Immunol 2005;115:584-91.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al (2006) Second Symposium on the Definition and Management of Anaphylaxis: Summary Report - Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. Ann Emerg Med;47(4):373-80.

Schaefer, J.L. (1997). Analysis of Incomplete Multivariate Data, Chapman&Hall.

Ulm K (1990). A simple method to calculate the confidence interval of a standard mortality ratio. American Journal of Epidemiology, 131(2); 373-375

Weisman S, Pollack CR, Gottschalk RW (2003) Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. J Dermatology Treat; 14: 158-165.