NOVARTIS

Clinical Development

AIN457/ Secukinumab/Cosentyx®

CAIN457M2302

# A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE)

Statistical Analysis Plan (SAP) Final Week 52 Analysis

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## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine aminotransferase |
| AN | Abscesses and inflammatory nodules |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Classification |
| COVID-19 | Coronavirus disease of 2019 |
| CM | Concomitant Medication |
| CRF | Case Report Form |
| CSR | Clinical Study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| EOT | End of Treatment |
| EQ-5D | EuroQol-5 Dimension |
| FAS | Full Analysis Set |
| GGT | Gamma-Glutamyl Transferase |
| HLT | High Level Term |
| HS | Hidradenitis suppurativa |
| HS-PGA | Hidradenitis Suppurativa Physician's Global Assessment |
| ICE | Intercurrent event |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MAR | Missing at random |
| MELRM | Mixed Effect Logistic Regression Model |
| mHSS | modified Hidradenitis Suppurativa Score |
| MMRM | Mixed Model for Repeated Measures |
| NRS | Numerical Rating Scale |
| PD | Pharmacodynamic(s) |
| PFS | Pre-filled syringe |
| PGI-c | Patient Global Impression of change |
| PGI-s | Patient Global Impression of severity |
| PK | Pharmacokinetics |
| PRO | Patient-reported Outcomes |
| QoL | Quality of Life |
| Q2W | Once every two weeks |
| Q4W | Once every four weeks |
| RAP | Report and Analysis Process |
| RDO | Retrieved drop-out |
| RMP | Risk management plan |
| SAP | Statistical Analysis Plan |
| SCC | Skin squamous cell carcinoma |
| S.C. | Subcutaneous |

| | |
|---|---|
| SAE | Serious adverse event |
| SOC | System Organ Class |
| TS | Trial statistician |
| TFL | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis for the following study:

CAIN457M2302 - A randomized, double-blind, multicenter study assessing short (16 weeks) and long-term efficacy (up to 1 year), safety, and tolerability of 2 subcutaneous secukinumab dose regimens in adult patients with moderate to severe hidradenitis suppurativa (SUNSHINE).

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 the final Week 52 analysis after all subjects have completed the study.

All analysis related to the primary and secondary objectives in the testing hierarchy are described in the Week 16 Primary Endpoint Analysis (PEA) SAP and are not covered in this final Week 52 SAP. The study and list of primary, secondary and exploratory objectives are kept for background.

[redacted]

## 1.1 Study design

This is a multicenter, randomized, double-blind, placebo controlled, parallel group study with two secukinumab dose regimens planned in approximately 541 subjects with moderate to severe hidradenitis suppurativa (HS).

The study consists of: Screening (up to 4 weeks), Treatment Period 1 (16 weeks) and Treatment Period 2 (36 weeks; optionally extended up to 48 weeks in case of pandemic major disruptions). Subjects who prematurely discontinue the study, or who complete the study and do not wish to continue in an optional extension study, will need to complete a post-treatment Follow-Up period (8 weeks).

Subjects will be randomized at a 1:1:0.5:0.5 ratio to one of four treatment arms at the time of randomization (baseline) visit:

- Secukinumab 300 mg every 2 weeks
- Secukinumab 300 mg every 4 weeks
- Placebo to secukinumab 300 mg every 2 weeks
- Placebo to secukinumab 300 mg every 4 weeks

Approximately 180 subjects are planned to be randomized to each of the two secukinumab arms and another approximately 180 subjects are planned to be randomized to the two placebo to secukinumab arms. Randomization will be stratified by region, current antibiotic use and body weight.

Subjects who complete Treatment Period 1 will enter Treatment Period 2. At Week 16, subjects who were randomized to one of the two secukinumab arms will continue on the same dose. Subjects who were randomized to the two placebo to secukinumab arms will start either

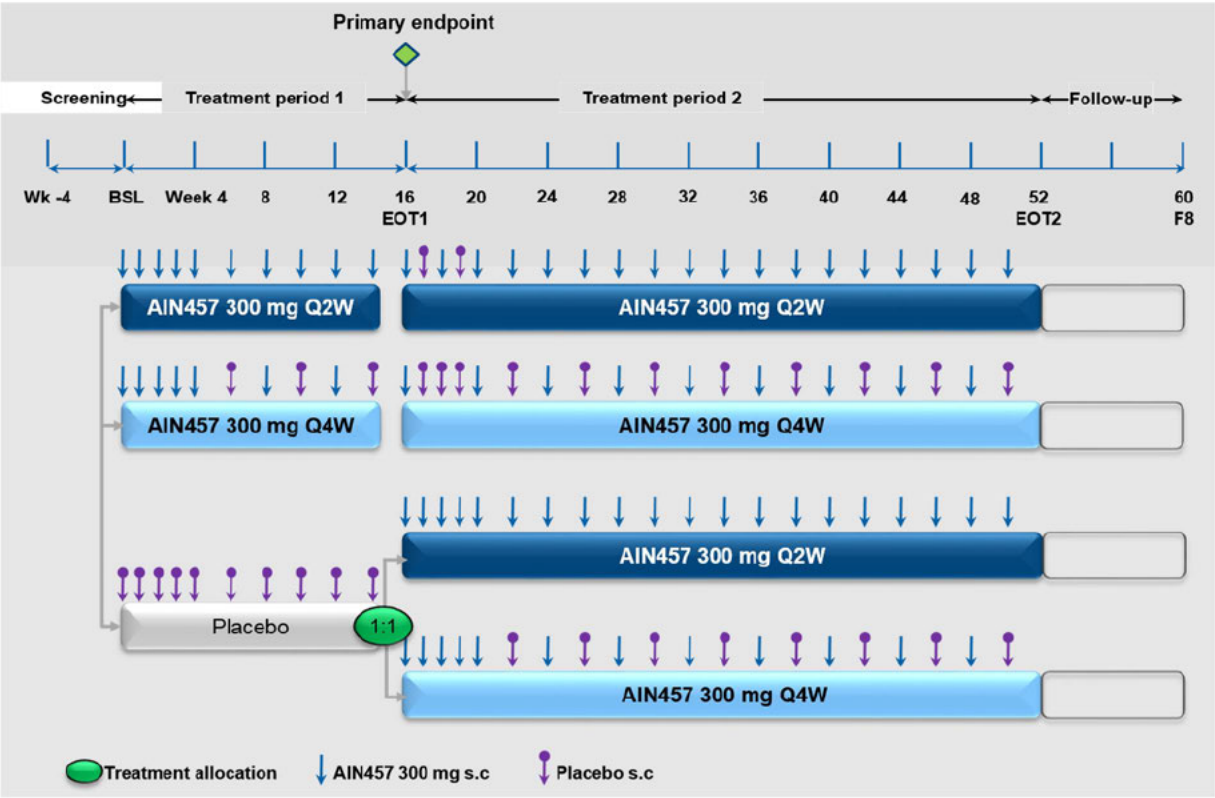
secukinumab 300 mg every 4 weeks or secukinumab 300 mg every 2 weeks according to their treatment arms definition.

The planned end of Treatment Period 2 visit (EOT 2) will be performed at Week 52. At this visit, the site should call Interactive Response Technology (IRT) after performing the scheduled study assessments to record the completion of the Treatment Period for the subject(s). For subjects rolling over to the optional extension study, Week 52 will be the end of study visit; for subjects continuing to the post-treatment Follow-Up period, the visit at Week 60 will be the end of study visit.

Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 52 should not be considered discontinued from the study. Subjects should continue attending site visits for the study assessments. Subjects who are unwilling to continue the further study visits after discontinuing the study drug should attend the end of study visit. The End of Treatment visit (EOT 1 for discontinuation during Treatment Period 1 and EOT 2 for discontinuation during Treatment Period 2) should be performed two weeks (where possible) after their last dose of study drug. After the EOT visit, subjects should enter the post-treatment Follow-Up period.

Only subjects who prematurely discontinue the study in Treatment Periods 1 or 2 for any reason, or subjects who do not enroll in the extension study will enter the post-treatment Follow-Up and potentially complete the Week 60 visit.

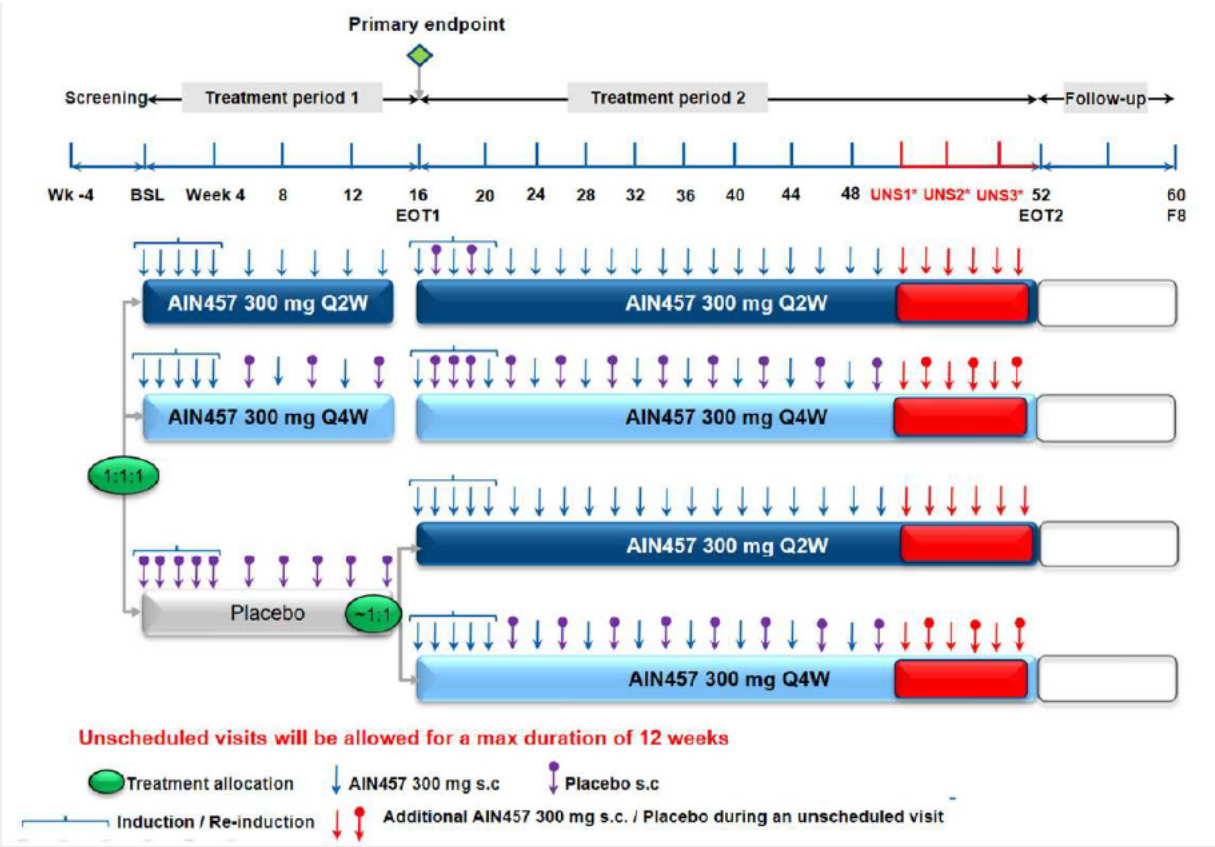
**Figure 1-1 Study design**



BSL: Baseline; EOT1/EOT2: End of Treatment 1/2; q2w: every two weeks; q4w: every four weeks. Treatment allocation for Placebo arm switching to secukinumab arms at Week 16 will be performed at the Randomization visit in 1:1 ratio and does not account for potential discontinuations during Treatment Period 1. Follow-Up: only subjects who prematurely discontinue treatment during Treatment Period 1 or 2 or subjects who do not enroll in the extension study, will enter Follow-Up.

In the event Week 52 cannot be performed on-site as scheduled due to a global health disruptive event, such as a pandemic/epidemic (e.g. COVID-19), or to a delay of HAs/ECs approval of the extension protocol, an additional treatment period of up to a maximum of 12 weeks (i.e., up to 6 doses, the frequency of study drug injections will remain every 2 weeks) could be considered to ensure therapeutic continuity for the patients until they are able to perform Week 52 visit onsite, and then participate in the long-term extension study.

**Figure 1-2 Study design in case of global health disruptive event.**




*UNS = Unscheduled; UNS1, UNS2 and UNS3 correspond to three possible additional IRT calls at which 2 doses will be dispensed.

The primary endpoint will be evaluated at Week 16, which is the maximum acceptable duration of treatment exposure to placebo in this indication. The total study duration, including one year of treatment, will allow for assessment of long term safety and sustainability of the effect in the two secukinumab dose regimens.

[redacted]

[redacted]

A primary endpoint analysis (PEA) is planned after all subjects have completed the visit at Week 16 for regulatory submission. At the time of the primary endpoint analysis, the designated Novartis personnel (e.g. biostatisticians and programmers involved in the analysis, key Global Team members) may have access to the unblinded results. Field monitors/clinical research associates will remain blinded until final database lock. Subjects and site personnel directly involved in the conduct of the trial, i.e. investigator staff and persons performing the assessments, will remain blinded to individual treatment allocation until the conclusion of the study to ensure study integrity is maintained.

[redacted]

At the end of the study, a final analysis will be performed when all subjects have completed their last visit in the study and this is the focus of this SAP.

## 1.2 Study objectives, endpoints and estimands

[redacted] Table 1-1 describes the objectives and related endpoints [redacted]

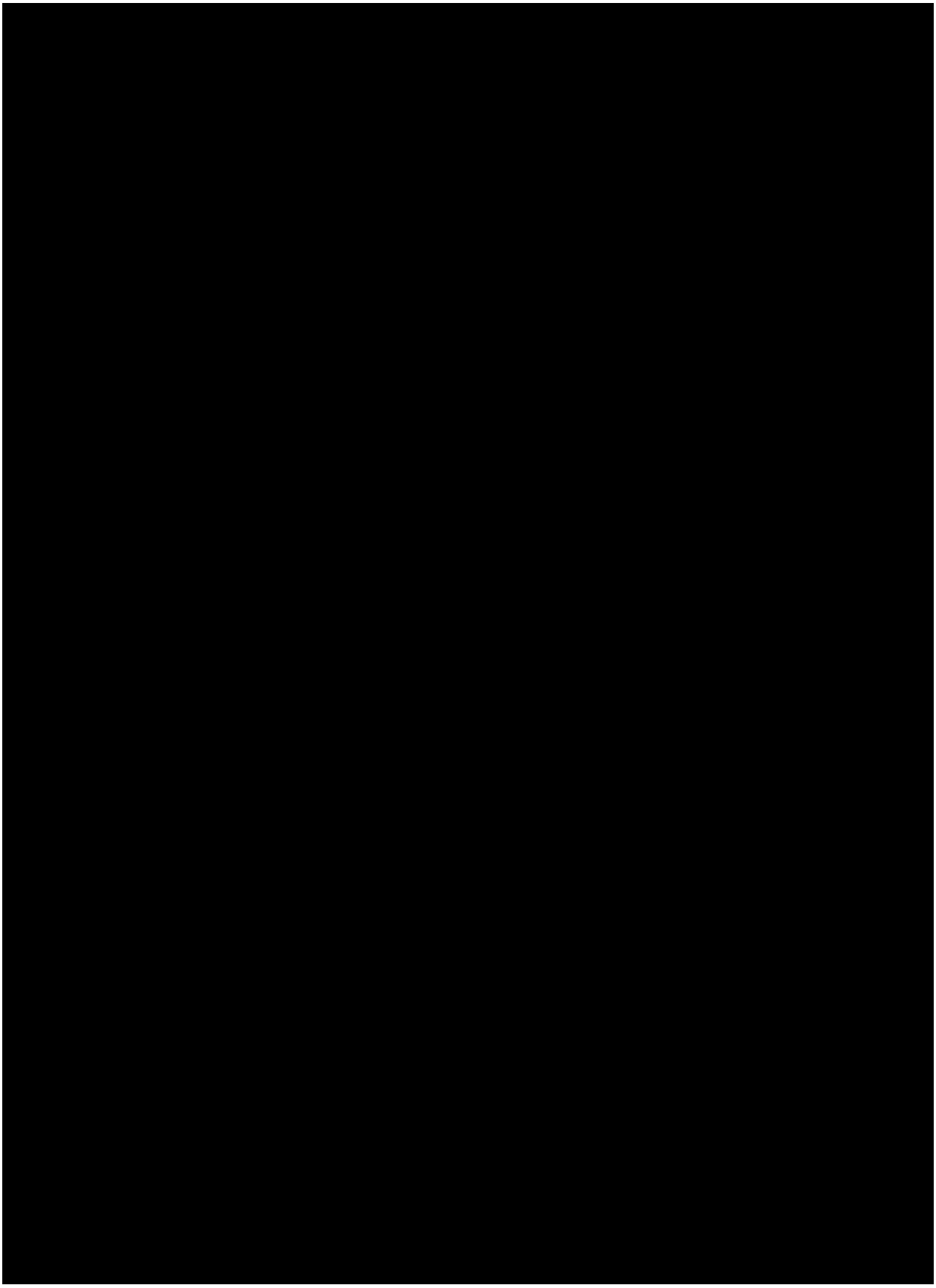
**Table 1-1 Objective and related endpoints** [redacted]

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To demonstrate the efficacy of secukinumab compared to placebo with respect to HiSCR after 16 weeks of treatment. | • Achievement of HiSCR at Week 16. HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the number of draining fistulae. |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To demonstrate the efficacy of secukinumab compared to placebo after 16 weeks of treatment with respect to AN count.<br>• To demonstrate the efficacy of secukinumab compared to placebo with respect to:<br>  ◦ proportion of subjects with HS flares<br>  ◦ proportion of subjects with clinical response in HS related skin pain | • Percentage change from baseline in AN count at Week 16.<br>• Flaring up to Week 16. Flare is defined as at least a 25% increase in AN counts with a minimum increase of 2 AN relative to baseline.<br>• Achievement of NRS30 at Week 16, among subjects with baseline NRS ≥ 3. |

| Objective(s) | Endpoint(s) |
|---|---|
| | NRS30 is defined as at least a 30% reduction and at least 2 units reduction from baseline in Patient's Global Assessment of Skin Pain - at worst. |
| **Exploratory objective(s)** | **Endpoint(s) for exploratory objective(s)** |
| • To evaluate the safety and tolerability of secukinumab over 52 weeks of treatment. | • Clinical safety and tolerability assessments:<br>  • physical exams,<br>  • vital signs,<br>  • laboratory assessments,<br>  • AE monitoring |
| • To explore the long-term effect of secukinumab with respect to HiSCR, AN count, proportion of subjects with flares, HS related skin pain up to 52 weeks of treatment. | • Achievement of clinical response as defined by HiSCR, HiSCR25, HiSCR50, HiSCR75, HiSCR90, HiSCR100.<br>• Absolute/percent and percentage change from baseline in AN count, AN (0/1), AN25, AN 50, AN75, AN90, AN100 response.<br>• Flares.<br>• Achievement of pain relief as defined by NRS30. |
| • To evaluate the effect of secukinumab with respect to the following efficacy assessments:<br>  • Modified Hidradenitis Suppurativa Score (mHSS);<br>  • HS-Physician's Global Assessment (HS-PGA);<br>  • Dermatology Life Quality Index (DLQI);<br>  • Health Status Questionnaire (EQ-5D-3L);<br>  • Patient Global Impression of severity (PGI-s);<br>  • Patient Global Impression of change (PGI-c);<br>  • Work Productivity Activity Impairment (WPAI);<br>  • HS Symptom Diary<br>  • Inflammatory markers with respect to CRP and ESR<br>compared to placebo after 16 weeks and in the two secukinumab dose regimens up to 52 weeks of treatment. | • Absolute and percent change from baseline in modified Hidradenitis Suppurativa Score (mHSS).<br>• HS-PGA response. HS-PGA response is defined as the achievement of at least a 2-point reduction in HS-PGA score compared to baseline.<br>• DLQI response and absolute/percent DLQI total score change from baseline. DLQI response is defined as a decrease greater than 5.0 points from baseline in DLQI total score.<br>• EQ-5D-3L Categories on Category questions and summary statistics on EQ - 5D -3L score questions.<br>• Patient Global Impression of severity and change (PGI-s and PGI-c) categories.<br>• Absolute and percent change from baseline in Work Productivity and Activity Impairment - Specific Health Problem (WPAI-SHP).<br>• HS Symptom Diary items score change from baseline. |

| Objective(s) | Endpoint(s) |
|---|---|
| | • Absolute and percent change from baseline in CRP and ESR. |
| • To evaluate the pharmacokinetics of secukinumab in HS subjects. | • AIN457 levels in serum |
| • To assess the development of immunogenicity against secukinumab. | • anti-AIN457 antibodies levels in serum |
| • To explore the potential association of biomarker levels with secukinumab efficacy and safety by visit up to Week 52 (EOT2). | • Biomarkers in serum |
| • To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment, and the sustained efficacy over time in bio-naive patients. | • Achievement of HiSCR at Week 16 and up to Week 52 in bio-naive patients. |
| • To explore the efficacy of secukinumab compared to placebo with respect to HiSCR response after 16 weeks of treatment and the sustained efficacy over time in patients with body weight lower and higher than 90 kg (<90 kg and ≥90 kg). | • Achievement of HiSCR at Week 16 and up to Week 52 in patients with body weight lower and higher than 90 kg (<90kg and ≥90kg). |

[redacted]



### 1.2.1 Estimand

The estimand framework relating to the primary and secondary estimands are described in the Week 16 PEA SAP.

# 2 Statistical methods

## 2.1 Data analysis general information

Novartis will be performing the analysis. Statistical software SAS version 9.4 or later will be used.

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. Unless otherwise stated, summary tables/figures/listings will be based on all subjects included in the population under consideration.

Listings will be presented by treatment arms.

Footnotes will generally be provided for:

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

Footnotes will generally NOT be given for

- units displayed on the output

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

### 2.1.1 Study Day 1 and other study days

Day 1 is the day of the first drug administration of the study treatment (or randomization day if there has been no drug administration).

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

### 2.1.2 Screening, baseline and post-baseline definitions

*Screening* refers to any procedures (e.g., checking inclusion and exclusion criteria) performed prior to the first dose of study treatment. 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 first dose.

#### Baseline definitions

For efficacy analyses,

- For HS Symptom Diary assessment and Patient's Global assessment of Skin Pain, the average of the latest 7 assessments before the date of the first drug administration of the study treatment (or randomization date if there has been no drug administration) will be used as baseline. In case less than 4 diary entries prior to the first dose of the study treatment were available, baseline will be set to missing.
- For all other efficacy assessments, baseline is the last assessment (including unscheduled visits) obtained (on or) before the day of the first drug administration of the study treatment (or randomization date if there has been no drug administration).

All assessments obtained after first dose (day) of study treatment 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 first dose day, exact dosing time is not considered.

### 2.1.3 Day of last dose of study treatment

The date of last dose will be collected via the CRF.

The subject's exposure will be calculated considering the last visit or the last dose + 84 days whichever occurs earlier.

## 2.2 Analysis sets

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

The **Randomized Analysis Set (RAN)** consists of all randomized subjects. Subjects will be analyzed according to the treatment they are assigned to at randomization. Unless otherwise specified, misrandomized patients (mis-randomized in IRT) are excluded from the randomized set.

Mis-randomized patients are patients who were screen-failures, but had been randomized by the investigator before eligibility was finally assessed, however had not been treated.

Furthermore, all subjects with serious GCP violation at their site will be excluded from the randomized set.

The **Full Analysis Set (FAS)** consists of all subjects to whom study treatment has been assigned. Subjects will be analyzed according to the treatment assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) and subjects with serious GCP violation at their site will be excluded from FAS. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

The **Safety Set (SAF)** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received. Treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received (subject received the wrong treatment during the entire study). Mis-randomized subjects and subjects with serious GCP violation at their site will be excluded from the safety set.

## 2.3 Analysis period and treatment groups

### 2.3.1 Final Week 52 analysis

The efficacy and safety analyses will be conducted up to Week 52 or Week 60, when all subjects have completed the study.

The efficacy will be conducted using the following treatment groups:

- AIN457 300mg Q2W (subjects randomized to secukinumab 300 mg every 2 weeks arm)
- AIN457 300mg Q4W (subjects randomized to secukinumab 300 mg every 4 weeks arm)
- PBO-AIN457 300mg Q2W (subjects randomized to placebo who switched to secukinumab 300 mg every 2 weeks arm at Week 16. Data is included after first intake of placebo.)
- PBO-AIN457 300mg Q4W (subjects randomized to placebo who switched to secukinumab 300 mg every 4 weeks arm at Week 16. Data is included after first intake of placebo.)

The safety will be conducted using the following treatment groups:

- AIN457 300mg Q2W (subjects randomized to secukinumab 300 mg every 2 weeks arm)
- AIN457 300mg Q4W (subjects randomized to secukinumab 300 mg every 4 weeks arm)
- Any AIN457 300mg Q2W (subjects randomized to secukinumab 300mg Q2W plus subjects randomized to placebo to secukinumab 300 mg every 2 weeks arm after their first intake of secukinumab)
- Any AIN457 300mg Q4W (subjects randomized to secukinumab 300mg Q4W plus subjects randomized to placebo to secukinumab 300 mg every 4 weeks arm after their first intake of secukinumab)
- Any AIN457 (this group combines the two groups “Any AIN457 300mg Q2W” and “Any AIN457 300mg Q4W”)

The subjects randomized to placebo to secukinumab 300 mg every 2 weeks arm and placebo to secukinumab 300 mg every 4 weeks arm will be counted in placebo until the day before the first secukinumab dose. Subsequently, they will be counted in Any AIN457 300mg Q2W or Any AIN457 300mg Q4W, respectively. AEs that occur starting on the day of taking the first secukinumab dose will be counted in Any AIN457 300mg Q2W or Any AIN457 300mg Q4W; other assessments, (i.e. efficacy, lab assessments) collected on the day of taking the first secukinumab dose will be counted in the placebo group.

Safety tables related to exposure adjustment incident rate will also display the placebo treatement group.

## 2.4 Patient disposition, demographics and other baseline characteristics

Demographic and baseline characteristics will be summarized and listed based on the Randomized Analysis Set. The following background and demographic variables will be analyzed:

**Continuous variables:**

- Age
- Height
- Weight
- Body mass index (BMI)

**Categorical variables:**

- Age categories (<20, [20, 30), [30, 50), ≥50)
- Age categories (<30, [30, 40), [40, 65), ≥65)
- Gender
- Weight categories (<70 kg, [70 kg, 90 kg), ≥ 90kg)
- Weight categories (<90 kg, ≥ 90kg)
- Race
  - White
  - Black or African American
  - Asian
  - Native Hawaiian or Other Pacific Islander
  - American Indian or Alaska Native
- Ethnicity
  - Hispanic or Latino
  - Not Hispanic or Latino
  - Not reported
  - Unknown
- Smoking status at baseline
- Region
- Current antibiotic use (Yes/No)

Hidradenitis suppurativa specific baseline characteristics and history of disease will be summarized:

**Continuous variables:**

- Baseline AN count
- Baseline inflammatory nodule count
- Baseline abscess count
- Baseline draining fistula count
- Baseline total fistulae count
- Baseline NRS
- Baseline Hidradentis Suppurativa Physician's Global Assessment (HS-PGA)
- Baseline modified Hidradenitis Suppurativa Score (mHSS)
- Baseline hsCRPBsl ESR

- Dermatology Life Quality Index (DLQI) total score
- EuroQol-5 Dimension (EQ5D)
- Time since diagnosis of HS
- Time since HS symptom(s) onset

**Categorical variables:**

- Baseline Hurley stage
- Prior surgery for HS
- Family history of HS
- Previous exposure to systemic biologic therapy
- Previous exposure to adalimumab
- Previous exposure to systemic antibiotics
- Previous exposure to non- biologic and non-antibiotic systemic therapy

*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 of the last value prior to first dose will be used as a baseline value. If there is no weight or height recorded prior to taking the study treatment, BMI will be missing.

Time since diagnosis of hidradenitis suppurativa will be calculated using the following formula:

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

Time since disease duration (defined as onset of symptom) will be calculated using the following formula:

$$\text{Time since onset} = (\text{inform consent date} - \text{Symptom(s) onset date} + 1)/365.25$$

The first diagnosis date of hidradenitis suppurativa and hidradenitis suppurativa symptom(s) onset 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 in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group in the randomized set.

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

### Patient disposition

The number and percentage of subjects in the Randomized Analysis Set who completed the entire treatment period and who discontinued the treatment prematurely (including the reason for discontinuation) will be presented for each treatment group. A listing will be also provided, and detail reason for discontinuation might be displayed if applicable.

For each protocol deviation, the number and percentage of subjects for whom the deviation applies will be tabulated. All protocol deviations will be presented by PD category as well as by PD sub category (PD short description).

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

### 2.5.1 Study treatment / compliance

The analysis of study treatment data will be based on the Safety Set.

The number of secukinumab and placebo doses 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 period of time will be displayed using the following categories: “any exposure”, “≥ 1 week”, “≥ 2 week”, “≥ 3 week” , “≥ 4 weeks”, “≥ 8 weeks”, “≥ 12 weeks”, “≥ 16 weeks”, “≥ 24 weeks”, “≥ 32 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 (including follow-up visits) 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 in the follow-up period or in the corresponding treatment period.

Duration of exposure (days) = min (end 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

#### 2.5.1.1 Visit windows

Visit windows will be used for the data that is summarized by visit. They are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. For subjects randomized to Placebo to secukinumab 300 mg every 2 weeks arm and Placebo to secukinumab 300 mg every 4 weeks arm, the day of taking the first secukinumab dose will also need to be taken into visit window consideration. Further information will be found in Study Programming Dataset Specifications (PDS). The visit windows are shown in Table 2-1. In these tables, the days are counted since the first dose of study treatment (study day 1). These visit windows apply to measurements taken at every visit. For assessments collected less often different visit windows will be applied as detailed below.

When visit windows are used, all visits will be re-aligned, i.e. they will be mapped into one of the visit windows. E.g., if the Week 4 visit of a subject is delayed and occurs on Day 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 below.

**Table 2-1 Assessment windows for scheduled visits for analyses based on the entire study period**

| 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 100-120 |
| Week 18 | 18 | 127 | Day 121-134 |
| Week 20 | 20 | 141 | Day 135-155 |
| Week 24 | 24 | 169 | Day 156-183 |
| Week 28 | 28 | 197 | Day 184-211 |
| Week 32 | 32 | 225 | Day 212-239 |
| Week 36 | 36 | 253 | Day 240-267 |
| Week 40 | 40 | 281 | Day 268-295 |
| Week 44 | 44 | 309 | Day 296-323 |
| Week 48 | 48 | 337 | Day 324-351 |
| Week 52 | 52 | 365 | Day 352-379 |
| Follow up | 60 | 421 | Starting from day 380 |

* Baseline measurement before the first drug administration.

For HiSCR, HiSCR components inflammatory nodules, abscesses, draining fistulae, Flare and other lesion related assessments, Screening 1 visit, Screening 2 visit and baseline visit will be adjusted per below table

| Analysis Visit | Week | Scheduled Day | Visit Window |
|---|---|---|---|
| Screening 1 | -4 | -21 | -28 days to -14 days |
| Screening 2 | -2 | -7 | -13 days to -1 days |
| Baseline | BSL | 1 | Day 1 |

For parameters which are not collected at every visit (e.g. weight, laboratory parameters, DLQI), visit windows defined in and Table 2-1 will be combined. The following rules are used to determine the visit window for an applicable visit post baseline: "Lower limit" = "upper limit of prior applicable visit" + 1. "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2. For example, if a parameter is measured at Baseline, Week 12 and Week 28 only, Week 12 visit window will extend from Day 2 to Day 141 (combining Week 1 to Week 20 visit windows), Week 28 will extend from Day 142 to Day 379 (combining Week 24 to Week 52). If more than one assessment falls into the interval, the rules defined below are applied.

The analysis visit will be used for listing of visit and period for both safety and efficacy data. If a visit falls after the last visit window (after Day 379) it is not assigned to an analysis visit and will be listed under label "After Week 52".

In case patients make use of the additional unscheduled visits for assessments other than the PGA of skin pain (NRS) before the Week 52 assessment (which were introduced due to the pandemic; see Section 1.1), the visit window for Week 52 and the follow-up period does not apply to these patients. The actual Week 52 visit will be taken for these patients as long as the time difference between this assessment and the last dosing is at most 4 weeks. The actual follow-up visit will be taken for these patients as long as the time difference between this assessment and the last dosing is at most 12 weeks.

For analysis of HS Symptom Diary assessment, Patient's Global assessment of skin Pain, the weekly average HS Symptom component score and NRS from Baseline to Week 52 is calculated based on the 7 available daily scores: Baseline (Week 0) will be average of HS symptom Diary score from day -7 to day -1, Week 1 will be average of score from day 1 to day 7, Week 2 will be average of score from day 8 to day 14 and so on. For any week with less than 4 diary entries within the week, the weekly average component score will be recorded as missing.

#### 2.5.1.2 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 2-2).

For baseline assessment definition see Section 2.1.2. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the scheduled day 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. DLQI response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

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

| Timing of measurement | Type of data | Rule |
|---|---|---|
| **Baseline** | All data | See Section 2.1.2 |
| **Post-baseline efficacy** | All data except for PRO e.g., HiSCR, HS-PGA | The measurement closest to the scheduled day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. |
| **Post-baseline efficacy** | PRO data | The measurement closest to the scheduled 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. For e-diary data, a cut-off at 3:00 PM is used to define the start of a new day. Anything entered before that time (no later than 2:59 PM) refers to the day before. If more than one measurement is taken on the same day (before the cut-off), the latest one will be used. |
| **Post-baseline safety** | Summary visit information (e.g. laboratory values, vital signs, etc.) | The (non-missing) measurement closest to the scheduled day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. |
| **Post-baseline 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. |

### 2.5.2 Prior and concomitant 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. Also, prior and concomitant treatments will be listed.

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 study treatment, and within 84 days after last dose will be a concomitant medication, including those which were started before first dose of study treatment and continued into the Treatment Period.

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Medications collected in ‘Prior HS Medications’ CRF page are considered as prior medications. Therapies collected on ‘Prior HS non-drug therapy’ CRF page are considered as prior therapies. Further rules will be given in Section 5.1.3.

Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by category and preferred term. Tables will

also show the overall number and percentage of subjects receiving at least one drug of a particular category and at least one drug in a particular preferred term.

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

Pain medication for HS (ibuprofen, tramadol and paracetamol) will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by category and preferred term. Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular category and at least one drug in a particular preferred term.

## 2.6 Safety analyses

All safety analyses will be based on the safety set.

Analysis of adverse events will be based on treatment emergent events, which are defined as events started on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days.

Other safety variables will be evaluated based on on-treatment events, which are defined as any events that happened after first dose of study treatment and on or before last dose + 84 days.

Safety analysis will be performed on actual treatment and the entire study period.

### 2.6.1 Adverse events (AEs)

For adverse events and other binary safety variables crude and exposure time adjusted incidence rates will be derived as described below and summarized in Table 2-3.

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

**Table 2-3 Overview of analyses on some safety endpoints**

| Analysis period | AEs & Risk management plans (RMP) | SAEs | AEs by severity | study treatment related AEs, death & other significant AEs | notables (lab/vitals) |
|---|---|---|---|---|---|
| Entire study period | • crude incidence<br>• exp.time adjusted incidence | • crude incidence<br>• exp.time adjusted incidence | • crude incidence | • crude incidence | • crude incidence |

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 5.4.2.1.

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. 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. AEs by severity will be provided by SOC and AEs by severity and PTs may be provided if required at ad-hoc basis.

The most common adverse events reported ($\geq z$% in any treatment group by SOC and PT) will be presented in descending frequency according to its incidence in Any AIN457 group starting from the most common event. The threshold value $z$ is set to 2 % but it may be updated following review of the dry run outputs.

Separate summaries will be provided for deaths, serious adverse events, other significant adverse events leading to discontinuation.

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

If for a same subject, 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 $\leq 1$ 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 AEs in a $\leq 1$ 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.

Algorithms for AE date imputations will be provided in Section 5.1.2.

### 2.6.2 Deaths

Separate summary and listing will be provided for deaths.

### 2.6.3 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 for the entire study period 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

All laboratory data will be listed with "on-treatment" flag displayed. In addition, Box and Whisker plots of hematology and serum chemistry will be provided for absolute values over time for Treatment period 1 and Entire study period.

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline within Treatment Period will be summarized analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the most extreme laboratory test value within 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 2-4: 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). CTCAE version 4.03 is implemented to be consistent with previous analyses.

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 2-4 CTCAE grades for laboratory parameters to be analyzed**

| CTCAE v4.03 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 period analyzed.

The number and percentage of subjects with newly occurring liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2-5.

**Table 2-5 Liver-related events**

| Parameter | Criterion |
|---|---|
| ALT | >3xULN; >5xULN; >8xULN;>10xULN, >20xULN |
| AST | >3xULN; >5xULN; >8xULN; >10xULN; >20xULN |
| ALT or AST | >3xULN; >5xULN; >8xULN; >10xULN; >20XULN |
| TBL | >1xULN;>1.5xULN; >2xULN; >3xULN, |
| ALP | >1.5xULN;>2xULN; >3xULN; >5XULN |
| ALT or AST & TBL | ALT or AST>3xULN & TBL >1.5xULN;<br>ALT or AST>3xULN & TBL >2xULN;<br>ALT or AST >5xULN & TBL >2xULN;<br>ALT or AST >8xULN & TBL >2xULN;<br>ALT or AST >10xULN & TBL >2xULN;<br>ALT or AST >20xULN & TBL >2xULN; |
| ALP & TBL | ALP >3xULN & TBL >2XULN<br>ALP >5xULN & TBL >2xULN |
| ALT or AST & TBL & ALP | ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Potential Hy's Law)<br>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.<br>ALT or AST>3xULN & TBL >2xULN & ALP <2xULN (Potential Hy's Law) or reported Hy's Law case<br>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 = 6.42x ULN is counted for ALT > 3x ULN and ALT > 5x ULN.

For urinalysis, all parameters collected will be listed.

### 2.6.4 Other safety data

#### 2.6.4.1 Vital signs

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for visits up to Week 52 will be performed by vital sign parameters 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

All vital signs will be listed with "on-treatment" flag displayed. In addition, Box and Whisker plots of hematology and serum chemistry will be provided for absolute values over time for Treatment period 1 and Entire study period.

The number and percentage of subjects with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2-6 below.

**Table 2-6 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 |

## 2.7 Pharmacokinetic endpoints

All subjects with quantifiable pharmacokinetic (PK) measurements of secukinumab will be included in the pharmacokinetic data analysis.

Serum concentrations will be expressed in mass per volume units. All concentrations below the limit of quantification as well as missing data will be labeled as such in the concentration data listings.

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

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

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

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

## 2.8 PD and PK/PD analyses

This analysis will be reported separately.

## 2.9 Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time.

## 2.10 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

## 2.11 Patient-reported outcomes

These analyses will use the FAS.

### Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific HRQoL measure presented to each subject from the randomization to the study end. The instrument contains six subscales (i.e. symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). For the DLQI, each of the 10 items is 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 subscales as well as the total score over all items. The higher the score, the more quality of life is impaired. The DLQI total score will be calculated by summing the score of each item resulting in a maximum of 30 and a minimum of 0. For details of DLQI scoring and interpretation please refer to Section 5.5.1.

Handling of missing values:

- Step 1: if there is only one item with missing score at a visit, it will be imputed as 0 and the subscale including this item and also the total score will be calculated accordingly.
- Step 2: If there are two or more items with missing scores at a visit, the scores for these two items will be missing, so is the subscale including this item and also the total score.

Summary statistics will be provided for absolute and percentage change from baseline of each of the six subscales as well as the total score by visit up to Week 52.

The DLQI scores as well as DLQI responders will be plotted over time. The median will be displayed for the DLQI score per visit and group. For DLQI responders, the rate will be calculated per visit and group and displayed as bar charts.

### Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP)

The WPAI-SHP has four subscales, which include Absenteeism, Presenteeism, Work Productivity Loss, and Activity Impairment.

The scores for these subscales are expressed as impairment percentages.

Questions:

1 = currently employed
2 = hours missed due to specified problem
3 = hours missed other reasons
4 = hours actually worked
5 = degree problem affected productivity while working
6 = degree problem affected regular activities

Scores: (Each of the below scores is multiplied by 100 to be expressed in percentages.)

- Absenteeism is the percent work time missed due to problem: Q2/(Q2+Q4)
- Presenteeism is the percent impairment while working due to problem: Q5/10

- Work Productivity Loss is the percent overall work impairment due to problem (absenteeism and presenteeism): Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]
- Activity Impairment is the percent activity impairment due to problem: Q6/10

Absolute change from baseline of WPAI component scores and the absolute WPAI component score will be provided by visit up to end of study.

### EQ-5D-3L

The EQ-5D-3L is a questionnaire with 5 questions (regarding mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each with three categories (no problem, moderate problem, severe problems) and a health state assessment from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of subjects in each of the three categories for each question will be presented by visit up to Week 52 for each treatment group. Summary statistics will be shown for absolute and percentage change from baseline of the health state assessment (VAS score) by visit up to Week 52 for each treatment group.

### PGI (PGI-s and PGI-c)

Summary statistics will be shown for absolute and percentage change from baseline of PGI-s and PGI-c by visit up to Week 52 for each treatment group.

### HS Symptom Diary

For analysis of HS Symptom Diary, the weekly average HS Symptom component score from baseline to Week 52 is calculated based on the 7 available daily scores: Baseline (Week 0) will be average of HS symptom Diary score from day -7 to day -1, Week 1 will be average of score from day 1 to day 7, Week 2 will be average of score from day 8 to day 14 and so on. For any week with less than 4 diary entries within the week, the weekly average component score will be recorded as missing. HS symptom Diary questions will be collected at specific visits only after Week 16 per pre-defined assessment schedule, thus HS Symptom component score after Week 16 is not provided as a weekly average but as single values. Statistics will be provided for absolute and percentage change from baseline of HS symptom component scores by visit up to Week 52 for each treament group.

#### Additional endpoints

Patient's Global Assessment of Skin Pain - at worst will be summarised on the original scale.

The analysis results on Patient assessed lesion count will be reported separately.

## 2.12 Biomarkers

All biomarker data will be listed by treatment group, subject and visit. Summary statistics will be provided by treatment and visit.

## 2.13 Other Exploratory analyses

Table 2-7 lists the primary, secondary and exploratory variables for this study. Unless otherwise specified in related sections, observed data will be used up to Week 52.

**Table 2-7 Exploratory variables**

| Variable | Type | Model | Missing data handling |
|---|---|---|---|
| HiSCR over time | exploratory | MELRM descriptive | use observed data only |
| Flare over time | exploratory | MELRM Kaplan Meier descriptive | use observed data only |
| AN count over time | exploratory | MMRM descriptive | use observed data only |
| AN50 over time | exploratory | MELRM descriptive | use observed data only |
| NRS30 over time | exploratory | MELRM descriptive | use observed data only |
| HiSCR25, HiSCR75, HiSCR90, HiSCR100 over time | exploratory | descriptive | use observed data only |
| AN25, AN50, AN75, AN90, AN100 AN 0/1, AN0/1/2 over time | exploratory | descriptive | use observed data only |
| No increase in draining fistulae over time | exploratory | descriptive | use observed data only |
| No increase in abcesses over time | exploratory | descriptive | use observed data only |
| Inflammatory nodules, abcesses, draining fistulale change from baseline over time | exploratory | descriptive | use observed data only |
| DLQI total score and component score over time | exploratory | descriptive | use observed data only |
| WPAI-HS over time | exploratory | descriptive | use observed data only |
| HS-dairy over time | exploratory | descriptive | use observed data only |
| PGI-s and PGI-c over time | exploratory | descriptive | use observed data only |
| EQ-5D | exploratory | descriptive | use observed data only |

Following analyses will use the FAS.

### Hidradenitis Suppurativa Clinical Response (HiSCR) components and alternative definitions

The number and percentage of HiSCR subjects will be presented by visit up to Week 52 for each treatment group, where HiSCR is defined as at least a 50% decrease in Abscess and Inflammatory Nodule (AN) count with no increase in the number of abscesses and/or in the

number of draining fistulae compared to baseline. Observed values will be presented for data up to Week 52.

Figures will be provided displaying estimates for responder rates by treatment groups including confidence intervals. The below lesion information will be presented by visit up to Week /52 for each treatment group. The number and percentage will be presented for subjects who achieved at least 25%, 50%, 75%, 90% and 100% reductions in the AN count relative to Baseline (AN25, AN50, AN75, AN90, AN100). Furthermore, the number and percentage will be presented for subjects who showed an AN count of either 0 or 1 (AN0/1) and for subjects who showed an AN count of either 0 or 1 or 2 (AN0/1/2).

- The number and percentage will be presented for subjects with no increase in the number of abscesses. Furthermore, the number and percentage of subjects with no increase in draining fistulae will be presented.
- Analogously, the number and percentage will be presented for subjects who achieved a slight modification of the HiSCR response: at least 25%, 75%, 90% and 100% reductions in the AN count with no increase in the number of abscesses and/or in the number of draining fistulae relative to baseline (HiSCR25, HiSCR75, HiSCR90, HiSCR100).
- Summary statistics will be presented for absolute and percent change from baseline for number of inflammatory nodules/abscesses/AN counts/draining fistulae. The following visualizations will be provided: The number of inflammatory nodules/abscesses/AN counts/draining fistulae will be plotted over time. For this, the mean will be provided per visit and group. Furthermore, the relative change from baseline in AN counts to Week 52 will be displayed per group using violin plots. Similarly, the absolute change from baseline in number of abscesses and draining fistulae to Week 52 will be displayed per group using violin plots.
- A mixed effects logistic regression model (MELRM) will be fitted. The endpoint is HiSCR at all time points from Week 2 up to Week 52 and are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### Percentage change from baseline in AN count

The mean change from baseline in AN count up to Week 52 will be presented for each treatment group. Observed values will be presented.

A mixed model for repeated measures (MMRM) will be fitted. The endpoint is percentage change from baseline in AN count and all time points from Week 2 up to Week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### Achievement of AN50

The number and percentage of AN50 up to Week 52 will be presented for each treatment group. Observed values will be presented.

Figures will be provided displaying estimates for AN50 rates by treatment groups including confidence intervals.

A similar MELRM analysis as described for HiSCR will be performed for this endpoint. The endpoint is the achievement of AN50 and all time points from Week 2 up to Week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### Flare

The number and percentage of Flare up to Week 52 will be presented for each treatment group. Observed values will be presented.

Figures will be provided displaying estimates for flaring rates by treatment groups including confidence intervals.

A Kaplan-Meier (KM) analysis for the cumulative incidence of the Flare-free period up to Week 52 will be presented for each treatment group. Observed values will be presented. Patients without Flare will be censored at the last known visit. Corresponding KM figures will also be provided.

A similar MELRM analysis as described for HiSCR will be performed for this endpoint.

rom Week 2 up to Week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### Skin Pain/NRS30

The number and percentage of NRS30 responder subjects will be presented by visit up to Week 52 for each treatment group observed values will be presented.

Figures will be provided displaying estimates for responder rates by treatment groups including confidence intervals.

A similar MELRM analysis as described for HiSCR will be performed for this endpoint.

The endpoint is the achievement of NRS30 and all time points for time windows from Week 2 up to Week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline NRS score and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If

additional convergence issues are encountered, then modifications to the model will be considered.

Analyses will be performed at a study level and also pooling both studies.

### Modified Hidradenitis Suppurativa Score

Summary statistics will be provided for absolute and percent change from baseline of modified Sartorius score by visit up to Week 52 for each treatment group.

### HS-Physician's Global Assessment

The number and percentage of subjects who achieve HS-PGA response will be presented by visit up to Week 52 for each treatment group, where HS-PGA response is defined as the achievement of at least a 2-point reduction in HS-PGA score compared to baseline or the achievement of a "mild" status (defined as achieving an HS-PGA score of $\leq 2$).

### CRP and ESR

Summary statistics will be provided for absolute and percent change from baseline of CRP and ESR by visit up to Week 52 for each treatment group.

## 2.14 Week 52 and Week 16 databases

Any changes to the Week 16 PEA HiSCR responder status as a result of changes to baseline or Week 16 lesion counts will be listed and assessed for the impact on the PEA. Additionally, any changes to the AN50 responder status, NRS30 responder status, flare and percentage change from baseline in AN count will be listed.

Changes to the treatment termination reason will also be listed in a separate listing.

Further, any new SAEs with start date prior to the cut-off date of the Week 16 PEA iDBL will be listed. All SAEs related to the Week 16 analysis that have been recorded or modified after the cut-off date and the SAEs with changed preferred term with start date prior to the cut-off date will be included.

# 3 Sample size calculation

Sample size requirements for this study are primarily driven by HiSCR at Week 16 endpoint. A 5% two-sided type-I-error rate will used to control for type-I-error. Two secukinumab doses will be tested versus placebo with respect to the primary endpoint (HiSCR at Week 16). The type-I-error will be split to 4% and 1% two-sided for secukinumab 300 mg Q2W vs. placebo and secukinumab 300 mg Q4W vs. placebo, respectively. Sample sizes will be based on this type-I-error assumption.

A total of 471 subjects was originally planned to be randomized to study drug in a 1:1:0.5:0.5 ratio. A second study of identical design with the same sample size will be conducted in parallel. Both studies are independently powered to address the primary endpoint (HiSCR) and secondary endpoints of AN count and flare. The secondary endpoint of pain will be analyzed in the combined populations of both trials, provided the primary null-hypothesis can be rejected in both studies. All sample size calculations were done in nQuery Advisor 7.0.

As discussed in Section 5 of the study protocol, to account for the disruptive impact of the COVID-19 pandemic on the conduct of the study since the release of protocol Amendment 01, the number of randomized subjects was increased to approximately 541 (15% increase from the original population of 471 subjects).

### Primary endpoint

HiSCR: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo response rate of 30% is assumed. The total sample size of 471 subjects for this trial is sufficient to achieve 93% power for the demonstration of 20% difference of secukinumab 300 mg Q2W over placebo based on the primary endpoint (HiSCR) when assuming a secukinumab response rate to be 50%. In regards to the comparison of secukinumab 300 mg Q4W to placebo, we achieve 83% power to show superiority. The sample size was further increased by 15% to 544 subjects to account for potential pandemic impact.

### Secondary endpoints

The power mentioned for the Secondary endpoints is conditional on the successful rejection of the null hypothesis for the primary endpoint (HiSCR), and the testing procedures are defined in Section 2.8 in the week 16 PEA SAP.

Percentage change in AN count: based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), it is assumed that the difference between secukinumab and placebo is at least 18% in favor of secukinumab when considering the mean percentage change from baseline in AN count at Week 16. Although it is planned to use an ANCOVA model for the analysis, an approximate sample size can be based on a simple $t$-test. A total sample size of 471 subjects is sufficient to achieve 92% power in secukinumab 300 mg Q2W vs. placebo and 81% power in secukinumab 300 mg Q4W vs. placebo when assuming a standard deviation of 46%.

Flare: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo rate of 35% is assumed. A total sample size of 471 subjects is sufficient to achieve 98% power for the demonstration of 20% difference of secukinumab 300 mg Q2W over placebo based on the second endpoint when assuming secukinumab 300 mg Q2W rate to be 15%. Assuming the same rate for secukinumab 300 mg Q4W, the sample size would be sufficient to achieve 92% power in a comparison of secukinumab 300 mg Q4W vs. placebo.

Pain: Based on adalimumab phase III placebo-controlled studies (PIONEER I and II, respectively, Kimball et al 2016), a placebo rate of 23% is assumed. Assuming 80% subjects are qualified to calculate Pain variable NRS30, a total sample size of 942 subjects across two studies is sufficient to achieve 85% power for the demonstration of 13% difference of secukinumab 300 mg Q2W over placebo based on the second endpoint when assuming the rate to be 36%. The sample size is also sufficient to achieve 70% power to demonstrate superiority of secukinumab 300 mg Q4W over placebo based on the same assumptions in regards to the rates of secukinumab and placebo as above.

# 4 Change to protocol specified analyses

Response of HS-PGA is defined as the achievement of at least a 2-point reduction in HS-PGA score compared to baseline or the achievement of a "mild" status (defined as achieving an HS-PGA score of ≤ 2). While in the Protocol it is defined as at least a 2-point reduction in HS-PGA score only.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Any partial dates will be imputed as follows:

The earlier day will be taken from below

- The last day in the month and
- The end day of the corresponding Treatment Period

### 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:

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

   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.

### 5.1.4 First diagnosis date and Symptom(s) onset date imputation

1. If the first diagnosis or Symptom onset day/ month are missing and the year is non-missing:
   a. If the year part of the date is equal to the year part of the inform consent date, then the imputed date is set to the year start point (01JANYYYY).
   b. Otherwise the imputed date is set to the mid-year point (01JULYYYY).
2. If the first diagnosis or Symptom onset day is missing and the month/year are non-missing:
   a. If the month and year part of date is equal to the month and year part of the inform consent date, then the imputed date is set to the month start point (01MONYYYY).
   b. Otherwise the imputed date is set to the mid-month point (15MONYYYY).

### 5.1.5 Other imputations

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

## 5.3 Laboratory parameters derivations

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests.

### Liver Function and Related Variables

Alanine transaminase (ALT) (SGPT): > 3 x Upper Limit of Normal (ULN)

Aspartate transaminase (AST) (SGOT): > 3 x ULN

Total bilirubin: > 2 x ULN

Alkaline phosphatase: > 2.5 x ULN

### Renal Function

Creatinine (serum): > 1.5 x ULN

**Hematology**

Hemoglobin: ≥ 2 g/dl decrease from baseline
Platelet count: < Lower Limit of Normal (LLN)
White blood cell count: < 0.8 x LLN
Neutrophils: < 0.9 x LLN
Eosinophils: > 1.1 x ULN
Lymphocytes: > 1.1 x ULN

**Urinalysis**

Protein urine dipstick: ++*
* ++ is ≥ 100 mg/dl

## 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. If applicable and not otherwise stated, means +/- SE will be plotted. If appropriate, summary statistics will also be derived for absolute and percentage changes from baseline.

#### 5.4.1.1 Mixed Model for Repeated Measures (MMRM)

A mixed effects regression model will be fitted. The endpoint is continuous and its values at all time points from Week 2 up to Week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### 5.4.2 Analysis of binary (and categorical) data

#### 5.4.2.1 Summary statistics for binary and categorical data

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

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

Then the lower limit is for $p > 0$ ($L = 0$ for $p = 0$):

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

and the upper limit is for for $p < 1$ ( $U = 1$ for $p = 1$):

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

Note: if $L > 100p$ then $L = 100p$ and if $U < 100p$ then $U = 100p$.

#### 5.4.2.2 Mixed effects logistic regression model (MELRM)

A mixed effects logistic regression model will be fitted. The endpoint is binary and all time points from week 2 up to week 52 are included on the left hand side of the model as dependent variables. The covariates included as fixed effects are: treatment group, visit, baseline AN count (or NRS for Skin Pain/NRS30) and the interaction between visit and treatment group. An unstructured covariance structure will be applied. In case of non-convergence, alternative covariance structures will be considered. If additional convergence issues are encountered, then modifications to the model will be considered.

### 5.4.3 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 $t_j$ $(j = 1, \ldots, n)$ 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 $\theta$. The rate parameter $\theta$ will be estimated as $\lambda = D/T$, 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 $100(1-\alpha)\%$ confidence interval for a Poisson variable with parameter $\theta T$ and observed value $D$ can be obtained based on (Garwood, 1936), from which an exact $100(1-\alpha)\%$ confidence interval for $\lambda = D/T$ will be derived as follows (Sahai, 1993; Ulm, 1990):

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

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

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

The example below shows how this should be handled for cases where subjects switch treatment. In particular for summarizing 'Any AIN' as a group, one should take into consideration the sequence of treatments while calculating exposure time for subjects.

**Table 5-1 Examples for calculating exposure time for incidence rates (IR)**

| 1st treatment | 1st exposure | 2nd treatment | 2nd exposure | Event days (in terms of study day) | Exposure for IR |
|---|---|---|---|---|---|
| Placebo | 100 days | 150 mg | 200 days | 50 (1st trt)<br>110 (10 days into 2nd trt) | Placebo: 50 days (event)<br>150 mg: 10 days (event)<br>Any AIN: 10 days (event) |

## 5.5 Patient reported outcomes

### 5.5.1 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item general dermatology disability index designed to assess Health-related quality of life in adult subjects with skin diseases (e.g. Hidradenitis Suppurativa). 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.

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.

### 5.5.2 Modified Hidradenitis Suppurativa Score

Collect lesion counts in all affected anatomic regions:

- Left axilla
- Right axilla
- Left groin
- Right groin
- Left gluteal
- Right gluteal
- Other

For each anatomic region, calculate the regional Sartorius score as follows.

Regional Sartorius Score = Region
+ 1 * Total noduli (=AN counts)
+ 6 * Total draining fistulae
+ Distance
+ Separate,

Where

Region =

3, if any lesion count in this anatomic region > 0

0, otherwise

Distance =

0, if no acitve lesions

1, if longest distance between two relevant lesions or size <5 cm

3, if longest distance between two relevant lesions or size 5-10 cm

9, if longest distance between two relevant lesions or size >10 cm

Separate =

0, with separation by normal skin

9, without separation by normal skin

The total Modified Hidradenitis Suppurativa Score would be the sum of all affected regional Hidradenitis Suppurativa Scores.

In case subjects make mistakes leading to missing data in region, total noduli (AN count), total fistulae, distance, or separate, the regional Hidradenitis Suppurativa Score will be set to missing and the same will be done for the total Modified Hidradenitis Suppurativa Score except for the two cases below:

- Total noduli is missing, region, total fistulae, distance, seperate is not missing, then noduli will be imputed as 0.
- Total fistulae is missing, region, total noduli, distance, seperate is not missing, then fistulae will be imputed as 0.

## 5.6 Rule of exclusion criteria of analysis sets

Table 5-2 presents the rules of exclusion criteria of analysis sets.

**Table 5-2 Subject Classification**

| Analysis Set | PD ID that cause subjects to be excluded | Non-PD criteria that cause subjects to be excluded |
|---|---|---|
| RAN | INCL01*, M-OTH07 | Not randomized/Mis-randomized |
| FAS | INCL01*, M-OTH07 | Not in RAN; |
| SAF | INCL01*, M-OTH07 | Not in RAN; No study drug taken |

* Written informed consent must be obtained before any assessment is performed.

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