NOVARTIS

Clinical Development

AIN457/Secukinumab / NCT02771210

[A randomized, double-blind, placebo-controlled multicenter study of subcutaneous secukinumab to demonstrate efficacy in the treatment of enthesitis at the Achilles tendon up to 1 year in adult patients with active Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) (ACHILLES)]

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted]

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23-Jun-2016	Prior to DB lock	Final version created		

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANCOVA	Analysis of covariance
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
[redacted]	[redacted]
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase
axSpA	axial Spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
[redacted]	[redacted]
CASPAR	Classification criteria for Psoriatic Arthritis
CRP	C-reactive protein
CSR	Clinical Study report
CTC	Common Toxicity Criteria
DMARD	Disease Modifying Anti-rheumatic Drug
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
[redacted]	[redacted]
hCG	human chorionic gonadotropin
hsCRP	High sensitivity C-Reactive Protein
IVR	Interactive Voice Response
IWR	Interactive Web Response
LEI	Leeds Enthesitis Index
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTX	Methotrexate
NRS	Numerical rating scale
PCS	Physical Component Summary
PFS	Prefilled syringe
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Imaging Score
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SF-36	Medical Outcome Short Form (36) Health Survey

SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TJC	Tender Joint Count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization

1 Introduction

This SAP module describes the planned statistical methods for all safety and efficacy analyses. Any changes made to the statistical plan and methodology after the clinical database lock will be documented as an addendum.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

Data will be analyzed by Novartis according to the data analysis section 9 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

This SAP describes the planned statistical methods. It is structured as

- A draft of the Clinical Study Report (CSR) Section 9.7 (statistical methods planned in the protocol and determination of sample size) and
- A draft of CSR Appendix 16.1.9 (documentation of statistical methods). Appendix 16.1.9 text will contain details of statistical methods and issues that are too long to include in the CSR text.

Please refer to the following document:

- Clinical Protocol CAIN457F3301

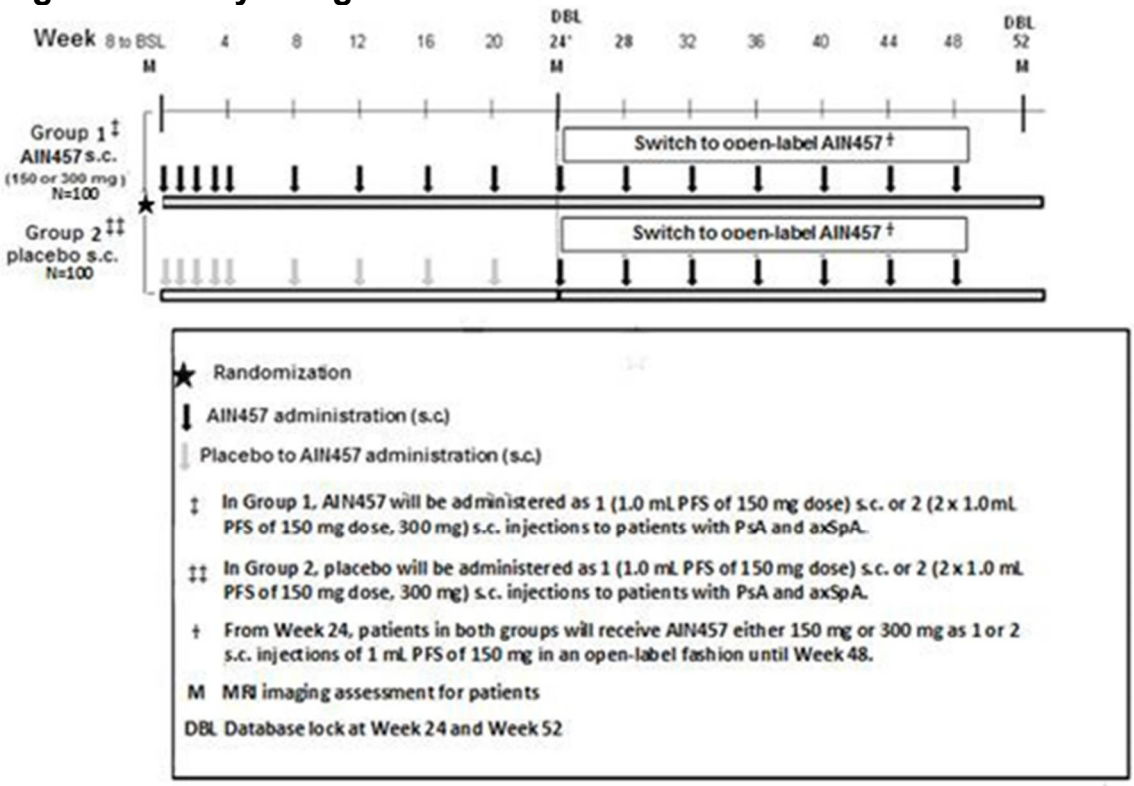
1.1 Study design

This is a 52-week, randomized, parallel-group, double-blind, multicenter, international study consisting of an 8-week screening period, a 24-week, placebo-controlled, double-blind treatment period and a 28-week open-label treatment period in patients with PsA and axSpA.

The dosing of secukinumab will be applied according to the approved European Summary of Product Characteristics (SmPC) in PsA and AS disease. According to SmPC, patients with AS and PsA (with concomitant none-to-mild psoriasis) will receive 150 mg secukinumab or placebo (1 PFS) where as only PsA patients with concomitant moderate-to-severe-psoriasis will receive 300 mg of secukinumab or placebo (2 PFS). In case of axSpA patients with objective signs of inflammation at screening, evident by either MRI with Sacroiliac joint inflammation (according to source documentation) and/or hsCRP > upper limit of normal (ULN, as defined by central lab) , secukinumab/placebo will be applied as 1 (1.0 mL pre-filled syringe (PFS) of 150 mg dose) s.c. injection.

The study design is given in Figure 1.

Figure 1: Study design



Planned number of patients and randomization

At Baseline approximately 200 patients will be randomized. Randomization will occur to one of the following two treatment groups in a ratio of 1:1.

- Group 1 (secukinumab): secukinumab as 1 (1.0 mL pre-filled syringe (PFS) of 150 mg dose) s.c. or 2 (2 × 1.0 mL PFS of 150 mg dose, 300 mg) s.c. injections according to axSpA or PsA disease at Baseline, Weeks 1, 2, and 3, followed by administration every 4 weeks starting at Week 4.
- Group 2 (placebo): placebo as 1 (1.0 mL PFS) or 2 (2 × 1.0 mL PFS) s.c. injections according to axSpA or PsA disease at Baseline, Weeks 1, 2, 3, followed by administration every 4 weeks starting at Week 4.

Patients will receive study treatment at Baseline, Weeks 1, 2, and 3, followed by treatment every 4 weeks through Week 52 (last dose given at Week 48). At Week 24, patients originally randomized to placebo will switch to receive secukinumab 150 mg (1 injection of secukinumab 1 mL/150 mg) or secukinumab 300 mg (2 injections of secukinumab 1 mL/150 mg) in open-label fashion without a loading regimen.

Blinding to the original treatment assignment will be maintained until after the Week 52 database lock and analyses are completed. However, original randomized treatment assignment to secukinumab or placebo will remain double-blinded to all patients, investigators, and site personnel, whereas the Sponsor (including the Region Europe Clinical Team, statisticians and data management) will be unblinded after the Week 24 database lock (protocol Section 3.5) and analyses are completed (protocol Section 9.7).

Patients will be stratified at randomization on the basis of PsA or axSpA disease.

Based on enrollment target, it is planned that approximately 50% of randomized patients should be PsA and approximately 50% axSpA patients to ensure a balanced patient population for the assessment of efficacy and safety.

Primary analysis time point

The primary analyses will be performed at Week 24.

Interim analyses

No interim analysis is planned for this study.

Once all data until/including Week 24 (containing the primary and secondary endpoints) are complete and clean, the database for that study period will be locked and analyzed. The results may be published or made available to personnel involved in data collection of this study prior to database lock of the complete study period until Week 52.

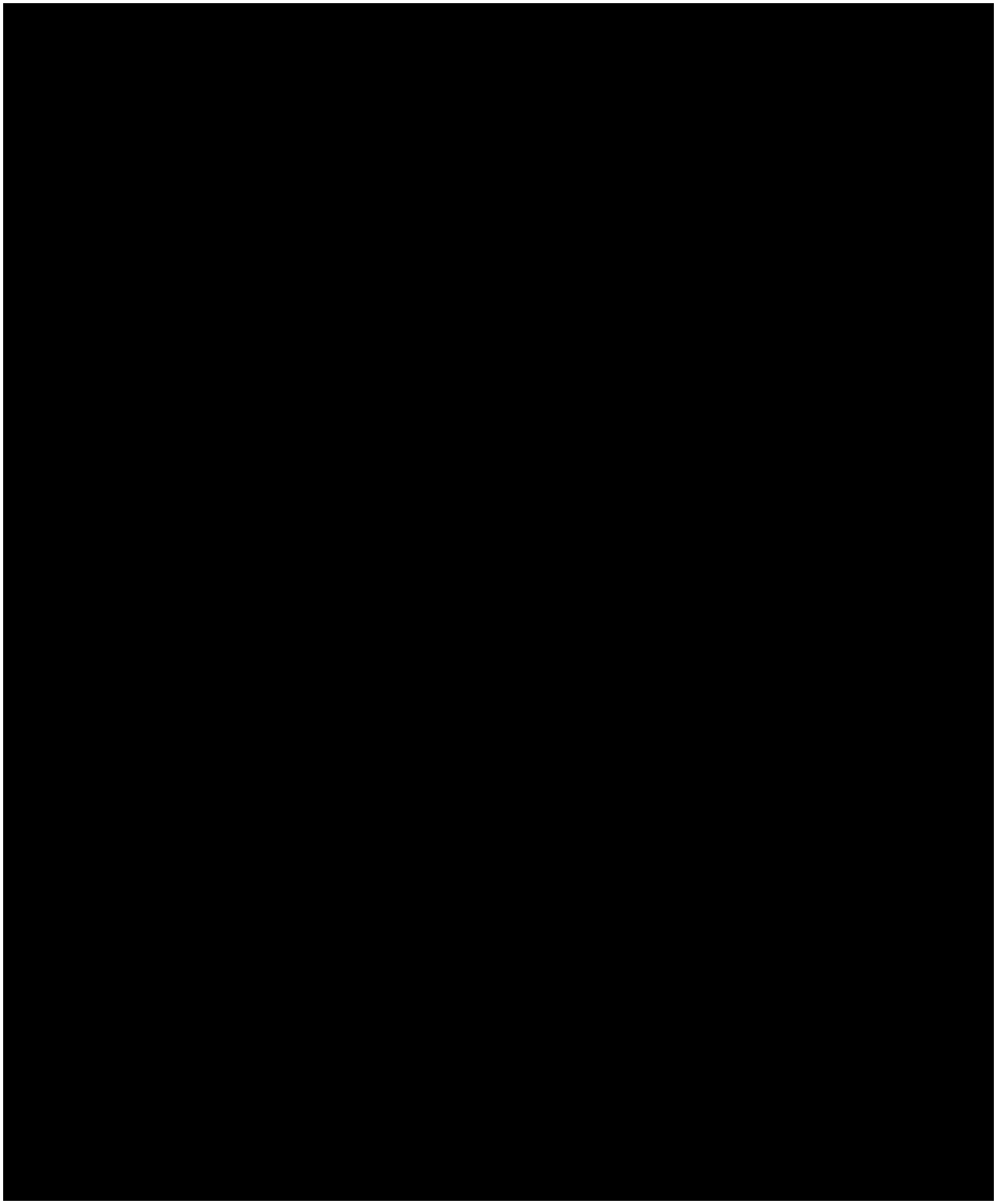
1.2 Study objectives and endpoints

The following objectives will be evaluated in patients with active PsA and axSpA.

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	
To demonstrate the superiority of secukinumab to placebo based on the respective subcomponent of LEI at 24 weeks in patients with active PsA and axSpA	Percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the LEI at 24 weeks
Secondary objectives	
To demonstrate the superiority of secukinumab to placebo at Week 24 based on the 10-point NRS	Mean change from baseline of heel pain measured on the 10-point NRS at Week 24
To demonstrate the superiority of secukinumab to placebo at Week 24 based on the respective subcomponent of PsAMRIS	Percentage of patients with an improvement of bone marrow oedema in the insertion of the Achilles tendon in the upper part of the calcaneus and/or in the insertion of the plantar aponeurosis in the lower part of the calcaneus as assessed by the respective subcomponent of the PsAMRIS at Week 24 in the affected foot at Baseline
To demonstrate the superiority of secukinumab to placebo at Week 24 based on the LEI	Percentage of patients with resolution of enthesitis as assessed by the LEI at Week 24

To demonstrate the superiority of secukinumab to placebo at Week 24 based on the physician's global assessment of disease activity	Mean change from baseline in physician's global assessment of disease activity at Week 24
To demonstrate the superiority of secukinumab to placebo at Week 24 based on the patient's global assessment of disease activity	Mean change from baseline in patient's global assessment of disease activity at Week 24
To demonstrate the superiority of secukinumab to placebo at Week 24 based on physician's global assessment of heel enthesiopathy	Mean change from baseline in physician's global assessment of heel enthesiopathy activity at Week 24
To demonstrate the superiority of secukinumab to placebo at Week 24 based on patient's global assessment of heel enthesiopathy.	Mean change from baseline in patient's global assessment of heel enthesiopathy activity at Week 24
To demonstrate the improvement in secukinumab to placebo at Week 24 based on SF-36 PCS or SF-36v2	Change from Baseline in SF-36 PCS or SF-36v2
To describe the improvement in resolution of Achilles tendon enthesitis after switching from placebo to secukinumab at Week 24.	Percentage of patients with resolution of Achilles tendon enthesitis in patients switching from placebo to secukinumab at Week 24.
To demonstrate the improvement of heel pain after switching from placebo to secukinumab at Week 24.	Mean change of heel pain in patients switching from placebo to secukinumab at Week 24
The overall safety and tolerability of secukinumab	Overall safety, as measured by frequency and severity of adverse events and changes in laboratory, vital signs and ECG values from baseline



2 Statistical methods

2.1 Data analysis general information

The analysis will be conducted by Novartis on all patient data after database lock for the respective trial periods. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Following the Week 24 database lock, the Sponsor will be unblinded to treatment assignment. Once all data until/including Week 24 (containing the primary and secondary endpoints) are complete and clean, the database for that study period may be locked and analyzed.

Continuous variables will be summarized by number of patients, mean, standard deviation, minimum, median and maximum. Categorical variables will be summarized by absolute and relative frequencies. Summary statistics will also be presented graphically wherever applicable.

If not otherwise specified, p-values and confidence intervals will be two-sided. Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

2.1.1 General definitions

Study treatment: Study treatment refers to:

Secukinumab 150 mg provided in 1 ml PFS or Secukinumab placebo provided in 1 ml PFS.

Study treatment start and end date: Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the core study.

Study day: Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g.visit, lab samples, AEs). For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1 and the day before study drug start date is study day -1 (i.e. no study day 0).

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for "time since event" data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1. Time from events prior to the start of study drug, e.g., time since diagnosis, is calculated as the difference between the start date of study drug and the date of prior event.

Note that, the first dose day is Day 1, and the day before the first dose day is counted as Day -1 (not Day 0).

Baseline and post baseline: In general, a *baseline* value refers to the last measurement made prior to administration of the first dose of study treatment. A post-baseline value refers to a measurement taken after the first dose of study treatment.

Treatment Period: There are two treatment periods for this study defined as :

Treatment Period 1 is defined as a 24 Week placebo-controlled, double-blind treatment period starting from baseline till Week 24.

Treatment Period 2 is a 28 Week open-label treatment period starting from Week 28 (end of Week 24) till Week 52.

Lost to follow up: The patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw.

On-treatment period: The period where the patients are exposed to the study treatment. For this study the treatment phase consists of 52 weeks (for treatment group 1) for secukinumab, and 24 weeks of on-treatment period for placebo and 28 weeks of on treatment for secukinumab (for treatment group 2).

2.2 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all patients who were randomized. Unless otherwise specified, miss-randomized patients (miss-randomized in IRT) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IVR prior to the site confirming all eligibility criteria had been met and to whom no study medication was given.

Full analysis set (FAS): The FAS will be comprised of all patients from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, patients will be evaluated according to the treatment assigned to at randomization. For patients randomized erroneously into the wrong stratum, the actual stratum will be used for analyses.

Safety set: The safety set includes all patients who took at least one dose of study treatment during the treatment period. Patients will be evaluated according to treatment received.

2.2.1 Subgroup of interest

The main subgroup of interest for this study are the PsA set of patients and axSpA set of patients. The two subgroups of PsA and axPsA patients will consist of approximately 50% in each of the total study population.

All (baseline, efficacy and safety) summaries will be performed based on this subgroup and overall.

A possible effect modification of patient characteristics will be explored by subgroup analyses for sex, age class and disease severity at Baseline.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and for all patients.

2.3.1 Patient disposition

The number and percentage of patients who are screened will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of patients who are enrolled, and who completed each treatment period and who discontinued the study will be summarized by treatment group at the end of each treatment period. In addition, for those patients who discontinued, the summary will be broken down by primary reason for study discontinuation.

The number and percentage of patients who took the rescue medication and hence discontinued at week 24 will be presented. For each protocol deviation (PD), the number and percentage of patients for whom the PD applies will be tabulated.

2.3.2 Demographics and other baseline characteristics

The following common background, demographics and baseline characteristics data will be analyzed as described below:

Continuous variables:

- Age (which is derived from date of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (<65 years, 65 – 74 years, 75 years and older)
- Gender
- Race
- Source of patient referral

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

- CASPAR, [redacted]
- Smoking status at baseline
- Disease background fo PsA/ axSpA, including time since diagnosis, etc
- Previous PsA/axSpA therapies
- PsA/axSpA functional status
- History of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis)
- Time since onset of inflammatory back pain
- Number and proportions of previous DMARDs used

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

2.3.3 Medical history

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.

Summaries for cardiovascular medical history and psoriasis and psoriatic arthritis history will be provided as well.

Smoking history will be summarized by treatment group.

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

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Study Treatment

The analysis of study treatment data will be based on the safety set. The number of active and placebo injections will be summarized by treatment group.

Duration of exposure

The duration of exposure to study treatment will be summarized by treatment group.

In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Duration of exposure will be defined as the time from first dose of study treatment to the time of treatment switch (for patients who switch treatment) or end of treatment period (whichever is first). For patients who discontinue, this will be the subject's last visit in the corresponding treatment period.

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 both the study treatment periods.

Compliance will be calculated based on documented study drug administrations and syringe counts and displayed by treatment group.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after enrolling into the study will be summarized by preferred term and ATC class of the World Health Organization (WHO) Drug Reference List.

Concomitant or prior medications entered into the database will be coded using the WHO Drug Reference List. Medical history/current medical conditions and AEs will be coded using MedDRA terminology.

Prior and concomitant therapies

Prior and concomitant medications will be summarized in separate tables by treatment group. Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of patients receiving prior and concomitant psoriatic arthritis therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to psoriatic arthritis therapies previously.

Prior or concomitant medication will be identified by comparing recorded or imputed start and end dates of medication taken to the reference start date.

Rescue medication

Rescue medication is defined as medication used to control symptoms that are not adequately controlled on study treatment.

No patient will be restricted from receiving necessary rescue medications for lack of benefir or worsening of disease, if rescue with prohibited treatments occurs prior to completion of Week 24 assessments, patients will be discontinued from the study.

Rescue medication will be summarized similarly to concomitant medication.

2.5 Analysis of the primary objective

The primary objective is to demonstrate that the efficacy of secukinumab is superior to placebo based on the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the Leeds enthesitis index (LEI) at 24 weeks in patients with active PsA and axSpA.

2.5.1 Primary endpoint

The primary endpoint is the percentage of patients with resolution of Achilles tendon enthesitis as assessed by the respective subcomponent of the LEI at Week 24. This resolution is referred to as ‘response’ below.

The analysis of the primary efficacy variable will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis to be rejected is that the odds of response Week 24 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 24 are higher under secukinumab compared to placebo.

In other words: Let pj denote the proportion of responders at Week 24 for treatment group j, j=0, 1, where

- 0 corresponds to placebo
- 1 corresponds to secukinumab

The following hypotheses will be tested:

H0: (p1 / (1- p1)) / (p0 / (1- p0)) = 1 versus H1: (p1 / (1- p1)) / (p0 / (1- p0)) $\neq$ 1

In other words, H1: The odds ratio of achieving a response at Week 24 for secukinumab vs Placebo is different from 1.

The hypothses can also be re-written as a difference of proportions as follows:

In statistical terms, H0: p1 = p0, H1: p1 $\neq$ p0, i.e.

H1: The difference of porportions at Week 24 for secukinumab vs Placebo is different from 0.

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, country and

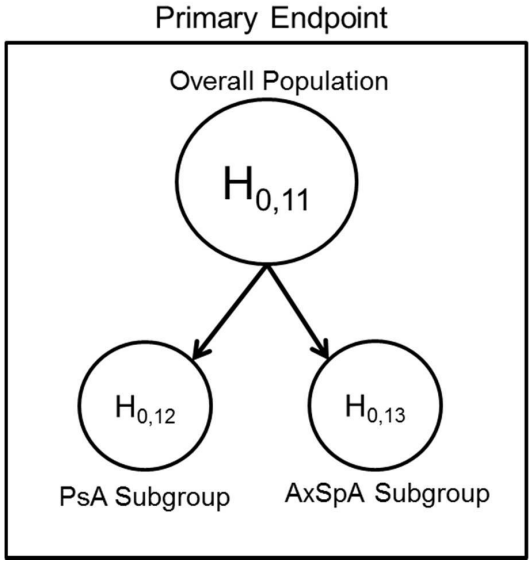
stratification factor diagnosis (PsA or axSpA). The odds ratio and its 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo at Week 24.

The study is said to be positive/declared as success if the lower limit of 95% CI of odds ratio is greater than 1.

The primary endpoint (percentage of patients with resolution of Achilles tendon enthesitis) will additionally be analyzed separately for the subgroups of patients with PsA or axSpA, using the same model as for the respective pooled, overall population tests (except for the stratification factor). Those two subgroup analyses are included in the confirmatory testing strategy. The primary model will also be recalculated with the stratification factor included as well as with respective term for a strata*treatment interaction.

Testing strategy

The primary endpoint will be confirmatorily tested in the pooled, overall population as well as in the two complementary subgroups of patients with PsA or axSpA.



If the null hypotheses has been rejected for the overall population, it will then be tested for both subgroups simultaneously, both at the significance level 0.05. If the null-hypothesis is false for the overall population, it can logically not be true for both complementary subgroups.

Therefore both subgroups can be tested at the same significance level $\alpha = 0.05$ without any further adjustments for multiplicity of subgroups. This procedure provides strong control of the familywise type-I-error at $\alpha = 0.05$.

2.5.3 Handling of missing values/censoring/discontinuations

This study aims to estimate the magnitude of treatment effects that are obtainable under the respective treatments. The disease activity is expected to decrease in the course of treatment. If a patient drops out or discontinues the trial prematurely, the last observed value of that patient seems to be a proper estimate for the effect achieved in that patient.

For the primary endpoint, a patient with a missing assessment will be considered as a responder if he/she has met the response criterion already at the time of drop-out. Otherwise he/she will be considered as a non-responder.

2.6 Analysis of the key secondary objective

Not applicable

2.7 Analysis of secondary efficacy objective(s)

Secondary objectives

Refer to Table 1-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

Secondary efficacy evaluation will be performed on FAS.

Refer to Table 1-1 of Section 1 for the list of secondary endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

The following hypotheses will be tested for the secondary objectives. All secondary endpoints will be tested exploratively outside the confirmatory framework:

H2: Secukinumab is not different to placebo regimen with respect to 10-point numerical rating scale (NRS) at Week 24.

H3: Secukinumab is not different to placebo regimen with respect to the respective subcomponent of the Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) in the affected foot at baseline at Week 24.

H4: Secukinumab is not different to placebo regimen with respect to resolution of enthesitis as assessed by the LEI at Week 24.

H5: Secukinumab is not different to placebo regimen with respect to physician's global assessment of disease activity at Week 24.

H6: Secukinumab is not different to placebo regimen with respect to patient's global assessment of disease activity at Week 24.

H7: Secukinumab is not different to placebo regimen with respect to physician's global assessment of heel enthesiopathy activity at Week 24.

H8: Secukinumab is not different to placebo regimen with respect to patient's global assessment of heel enthesiopathy acitivity at Week 24.

H9: The improvement in Secukinumab is not different to placebo regimen with respect to from Baseline in Short Form-36 Physical Component Summary (SF-36 PCS) or SF-36v2 at Week 24.

Analysis of secondary efficacy variables

- **Heel pain**

The mean change from Baseline of heel pain at 24 weeks, measured on a 10-point NRS will be analyzed using an Analysis of covariance (ANCOVA) model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline measuremenet of heel pain. The adjusted (LS) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

- **Bone marrow oedema (PsAMRIS)**

The percentage of patients with an improvement of bone marrow oedema will be analyzed using a logistic regression model with factors treatment, country and diagnosis (PsA or axSpA). The odds ratio and its 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo at Week 24.

- **Enthesitis Assessment (LEI)**

The 4-site LEI (i.e. score with the four correct sites: lateral epicondyle humerus L + R and proximal achilles L + R) will be analyzed using a logistic regression model with factors treatment, country and diagnosis (PsA or axSpA). The odds ratio and its 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo at Week 24.

- **Physician's global assessment of disease activity**

Physician's assessment, measured on a VAS scale will be analyzed using an ANCOVA model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline value of global assessment of disease activity. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

- **Physician's global assessment of heel enthesiopathy activity**

Physician's assessment, measured on a VAS scale will be analyzed using an ANCOVA model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline measurement of the global assessment of heel enthesiopathy. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

- **Patient's global assessment of disease and heel enthesiopathy activity**

Refer to section 2.11 for analyses details.

- **SF-36 or SF-36v2**

Refer to section 2.11 for analyses details

The time courses of secondary endpoints (percentage of patients with resolution of enthesitis as assessed by LEI, mean change from baseline for heel pain in NRS, Physician's / patient's

global assessment in VAS, etc.) will be summarized descriptively for all visits by treatment group, subgroup (PsA, axSpA) and overall from Baseline until Week 52.

Summary statistics will include relative and absolute frequencies for the binary variable 'resolution of enthesitis', and the number of patients (N), minimum, mean, median and maximum for the NRS/VAS variables. Additionally, these time courses will be displayed graphically.

Switching from placebo to secukinumab at Week 24

At Week 24, patients originally randomized to placebo will switch to receive secukinumab 150 mg (1 injection of secukinumab 1 mL/150 mg) or secukinumab 300 mg (2 injections of secukinumab 1 mL/150 mg) in open-label fashion without a loading regimen.

Summary statistics will be provided for:

- Number and percentage of patients with resolution of Achilles tendon enthesitis after switching from placebo to secukinumab at Week 24.
- Mean change of heel pain in patients after switching from placebo to secukinumab at Week 24.

2.7.3 Handling of missing values/censoring/discontinuations

This study aims to estimate the magnitude of treatment effects that are obtainable under the respective treatments. The disease activity is expected to decrease in the course of treatment. If a patient drops out or discontinues the trial prematurely, the last observed value of that patient seems to be a proper estimate for the effect achieved in that patient.

For the confirmatory analyses of secondary endpoints related to physician's/patient's global assessment and SF-36, missing values will be replaced by the last observed value in that patient (Last Observation Carry Forward). In case of a substantial number of missing values, alternative approaches (RMREM, MI) may be additionally calculated as sensitivity analyses.

2.8 Safety analyses

For all safety analyses, the Safety set will be used.

Summaries will be performed separately for first (Week 1-24) and entire treatment periods. Use of data up to and including the last visit before rescue provides and unbiased comparison between secukinumab and placebo; data collected beyond week 24 are included in analyses which summarize the entire treatment period.

Safety analyses will be performed by PsA and AxSpA patients on treatment received or actual treatment as described below:

The actual treatment or treatment received for summaries of safety data will differ to the treatment assigned at randomization only if a subject received the wrong treatment during the entire study.

For those patients who received not the treatment randomized, i.e. who received erroneously the wrong treatment at least once, an additional AE listing will be prepared displaying which events occurred after the treatment errors.

2.8.1 Adverse events (AEs)

The crude incidence of treatment emergent adverse events (i.e. events started 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) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in Section

In addition, exposure time-adjusted rates (incidence rate) including 95% confidence intervals will be provided for the entire treatment period to adjust for differences in exposure between treatment groups.Graphical displays of the crude incidence and exposure-adjusted rates will be presented for all AEs and serious AEs by system organ class.

Treatment emergent adverse events reported will be presented by preferred term in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event. Summaries (crude incidences only) 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 worst severity at the system organ class level, where applicable.

Separate summaries will be provided for

- adverse events suspected to be related to study drug by the investigator
- deaths
- serious adverse events
- adverse events leading to discontinuation
- adverse events leading to temporary dose interruption

Adverse events will also be reported separately by MedDRA SMQ.

For all adverse event summaries, the MedDRA version used for reporting the study will be described in a footnote.

Adverse event summaries will also be provided for the follow-up period for all patients (completers and early discontinuations).

A listing of non-treatment emergent adverse events will be provided. These cover adverse events that occurred before the first dose of the study treatment. The crude incidence will be provided without treatment information.

Algorithms for date imputations will be provided in Programming Specifications.

For SAEs that occurred during screening a listing will be prepared for all patients screened including screening failures.

Table 2.8-1 Overview of analyses on some safety endpoints

Analysis period	AEs & SAEs	AEs by severity	Study drug related AEs	AEs-SMQ	Risk	Notables for (vitals/ ECG), lab criteria
Day 1 – Week 24 Day 1 – Week 24	• crude incidence • exposure time adjusted incidence*	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire Treatment (up to week 52)	• crude incidence • exposure time adjusted incidence*	• crude incidence	• crude incidence	• exposure timeadjusted incidence	• crude incidence exposure time adjusted incidence	• crude incidence

*Exposure-adjusted incidence rates will be done for the following:

- at the PSOC for AE and SAE
- at the PT level for common AEs, which is defined as at least 2% of the patients in the combined AIN457 groups during the initial treatment period or events that had an incidence rate of at least 5.0 cases per 100 subject-years in the combined AIN457 groups during the entire treatment period
- at Level 1 for Risks and SMQ analyses

2.8.1.1 Adverse events of special interest / grouping of AEs

Safety topics of interest, such as risks defined in the Safety Profiling Plan (SPP), Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet that is stored in CREDI at the path Cabinets/CREDI Projects/A/AIN457A/Integrated Medical Safety.

The crude incidence and exposure-adjusted incidence rates for SPP risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

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

2.8.2 Deaths

Separate summaries and listings will be provided for deaths for each treatment period.

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented by patient sub-population for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from Baseline to each study visit will be presented in tabular and graphical fashion.

These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from Baseline will only be summarized for patients with both Baseline and Post-Baseline assessments.

For each parameter, the maximum change from Baseline within each study period will be analyzed analogously.

QuantiFERON TB-Gold test will also be analyzed by the central laboratory.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. If appropriate, the shifts to the most extreme laboratory test value within a treatment phase (either initial or entire) will be presented as well (including category "high and low"). These summaries will be presented by laboratory test and treatment group.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Table 2.8-2: Hematology will include hemoglobin, platelets, red blood cells (RBC), white blood cells (WBC), differential WBC counts. Serum chemistry will include glucose, cholesterol, triglycerides (TG), urea, creatinine, total bilirubin (TBL), AST (SGOT), ALT (SGPT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page.

These summaries will be split into hematology and chemistry for study level reports and the pooled summary of clinical safety.

Table 2.8-2 CTCAE grades for laboratory parameters to be analyzed

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 xULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Glucose increased (Hyperglycemia)	>ULN - 8.9 mmol/L	>8.9 - 13.9 mmol/L	>13.9 - 27.8 mmol/L	>27.8 mmol/L
Glucose decreased (Hypoglycemia)	<LLN - 3.0 mmol/L	<3.0 - 2.2 mmol/L	<2.2 - 1.7 mmol/L	<1.7 mmol/L
Cholesterol high	>ULN - 7.75 mmol/L	>7.75 - 10.34 mmol/L	>10.34 - 12.92 mmol/L	>12.92 mmol/L
Hypertriglyceridemia	1.71 - 3.42 mmol/L	>3.42 - 5.7mmol/L	>5.7 - 11.4 mmol/L	>11.4 mmol/L

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

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

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

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

Newly occurring or worsening liver enzyme abnormalities will also be summarized based on the event criteria given in Table 2.8-3:

Table 2.8-3 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>1.5xULN, >2xULN, >3xULN,
ALP	>2xULN, >3xULN. >5xULN
ALT or AST & TBL	ALT or AST>3xULN & TBL >2xULN; ALT or AST >5xULN & TBL >2xULN; ALT or AST >8xULN & TBL >2xULN; ALT or AST >10xULN & TBL >2xULN
ALP & TBL	ALP >3xULN & TBL >2xULN ALP >5xULN & TBL >2xULN

ALT or AST & TBL & ALP	ALT or AST>3xULN & TBL >2xULN & ALP<2xULN (Hy's Law) Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥2xULN may not result in severe DILI.
Notes: 1) In studies which enroll patients with pre-existing liver disease, baseline LFT may be increased above ULN; in such a case it is meaningful to add the condition "and worse than baseline" to the abnormality criteria.	

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

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

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The following quantitative variables will be summarized: ventricular rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Both Bazett (QTcB) and Fridericia (QTcF) corrections will be presented for QTc.

QTc will be summarized by computing the number and percentage of patients (including 95%confidence intervals for pooled analyses, e.g. DMC or SCS) with:

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

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

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

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

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. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

The number and percentage of patients with newly occurring notable vital signs will be presented. Criteria for notable vital sign abnormalities are provided in Table 2.8-4 below.

Table 2.8-4 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

2.8.4.3 Physical examination

Summary statistics will be provided for physical examination by visit.

2.8.4.4 Height and weight

Summary statistics will be provided for height and weight captured at screening.

2.8.4.5 Pregnancy and assessment of fertility

A serum β-hCG test will be performed in all women at Screening.

Urine pregnancy test will be performed at various visits as indicated in the assessment schedule

Summaries will be provided for both the above tests as other safety measures.

2.8.4.6 Tolerability of secukinumab

Tolerability will be assessed by AEs, laboratory values and injection site reactions and summarized accordingly.

2.9 Pharmacokinetic endpoints

Not applicable

2.10 PD and PK/PD analyses

Not applicable

2.11 Patient-reported outcomes

Patient's global assessment of disease activity

Patient's global assessment od disease activity, measured on a VAS scale will be analyzed using an ANCOVA model with factors treatment, country and diagnosis (PsA or axSpA) and

with covariate baseline measurement of the global assessment of disease activity. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

Patient's global assessment of heel enthesiopathy activity

Patient's global assessment of heel enthesiopathy, measured on a VAS scale will be analyzed using an ANCOVA model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline measurement of the global assessment of heel enthesiopathy. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

Short Form-36 Physical Component Summary (SF-36 PCS) or SF-36v2

The score of the SF-36 or SF-36v2 will be analyzed using an ANCOVA model with factors treatment, country and diagnosis (PsA or axSpA) and with covariate baseline value of SF-36 or SF-36v2. The adjusted (LS-) mean difference will be calculated as a point estimate together with its corresponding 95% confidence interval and p-value.

[redacted]

Bath ankylosing spondylitis disease activity index (BASDAI)

BASDAI wil be summarized descriptively for axSpA patients. Summary statistics will include relative and absolute frequencies.

2.12 Biomarkers

Not applicable

[redacted]

2.14 Interim analysis

Once all data until/including Week 24 (containing the primary and secondary endpoints) are complete and clean, the database for that study period will be locked and analyzed. The results may be published or made available to personnel involved in data collection of this study prior to database lock of the complete study period until Week 52.

The details of the Week 24 analyses will be mentioned in TFL Shells. Additional SAP for Week 24 analyses will be written if required.

3 Sample size calculation

The primary endpoint of this trial is the percentage of patients with resolution of Achilles tendon enthesitis assessed by application of firm pressure with the pulp of the thumb by the physician at Week 24. The sample size calculation is based on the same enthesitis assessment we performed within the FUTURE 2 PsA trial (CAIN457F2312) in the form of the LEI which is composed of three different enthesial sites (Lateral epicondyle, left and right; medial femoral condyle, left and right; Achilles tendon insertion, left and right). Within this trial, the resolution of enthesitis amongst those patients with these symptoms at Baseline has been assessed for Week 24:

Week 24, the end of the placebo-controlled phase:

- Secukinumab (300 mg): 48.2% of patients.
- Secukinumab (150 mg): 42.2% of patients.
- Placebo: 21.5% of patients.

In addition to these clinical data we can make the following assumptions:

- There is no difference in response to secukinumab between the different enthesial sites assessed as part of the LEI in the FUTURE 2 trial. Therefore we do not expect a different response when we only assess the Achilles tendon insertion.
- There is no difference in secukinumab response rates regarding resolution of enthesitis between PsA and axPsA patients. Therefore we pool the analysis for both diseases.

A total of 89 patients per arm are required to achieve 90% power to detect a difference on a two-sided, 2.5% significance level, if the true response rates are 45% under secukinumab and

21% under placebo. To account for some drop-outs and other protocol violations, 100 patients per arm = 200 patients total should be randomized into this trial.

For the comparison within the 2 subgroups of PsA and axPsA patients, which will consist of 50% of the total study population each, the trial will have about 46% power with regard to the primary endpoint.

No sample size justification is provided for secondary analyses, hence results from secondary analyses should be interpreted carefully.

4 Change to protocol specified analyses

Not applicable

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable

5.1.2 AE date imputation

AE date imputation is based only on a comparison of the partial AE start date to the treatment start date as mentioned in the Table 1-2 below.

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 the AE year is less than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if the AE year is less than the treatment year and the 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 year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
   b. Else if the AE year is greater than the treatment year and the AE month is not missing, the imputed AE start date is set to the month start point (01MONYYYY).
4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing or the AE month is equal to the treatment start month, the imputed AE start date is set to one day after treatment start.
   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 greater than the treatment start month, the imputed AE start date is set to the start month point (01MONYYYY).

Table 5.1-2: AE date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	NULL	NULL	NULL	NULL
	Uncertain	Uncertain	Uncertain	Uncertain
YYYY < CFY	(D) = 01JULYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY	(C)= 15MONYYYY
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	(B)= TRTSTD+1	(C)= 15MONYYYY	(A)= TRTSTD+1	(A)= 01MONYYYY
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	(E)= 01JANYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY	(A)= 01MONYYYY
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

5.1.3 Concomitant medication date imputation

Concomitant medication (CMD) date imputation uses both a comparison of the partial CMD start date to the treatment start date, and the value of the CMDTYP1C flag (1, 2, or 3). Event date comparisons to treatment start date are made based on the year and month values only (any day values are ignored) in Table 1-3 below.

1. If the CMD start date year value is missing, the date will be imputed based on the CMDTYP1C flag value. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date. (Note that for some legacy data, the CMDTYP1C variable may not exist in the data. When this happens and the CMD start date year value is missing, the imputed date value will be NULL.)
2. If the CMD start date year value is less than the treatment start date year value, the CMD started before treatment. Therefore:
    a. if the CMD year is less than the treatment year and the CMD month is missing, the imputed CMD start date is set to the mid-year point (01JulYYYY).
    b. Else if the CMD year is less than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the mid-month point (15MONYYYY).

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

    a. If the CMD year is greater than the treatment year and the CMD month is missing, the imputed CMD start date is set to the year start point (01JanYYYY).
    b. Else if the CMD year is greater than the treatment year and the CMD month is not missing, the imputed CMD start date is set to the month start point (01MONYYYY).

3. If the CMD start date year value is equal to the treatment start date year value:
    a. and the CMD month is missing or the CMD month is equal to the treatment start month,
        i. If the flag value is 1 or 3, the imputed CMD start date is set to one day before the treatment start date.
        ii. Else, if the flag value is missing or 2, the imputed CMD start date is set to one day after the treatment start date.
    a. Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to the mid-month point (15MONYYYY).
    b. Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to the start month point (01MONYYYY).

Table 5.1-3: CMD date imputation

	MON MISSING	**MON < CFM**	**MON = CFM**	**MON > CFM**
YYYY MISSING	**(F)**	**(F)**	**(F)**	**(F)**
	Uncertain	Uncertain	Uncertain	Uncertain

YYYY < CFY	**(D)=01JULYYYY**	**(C)=15MONYY**	**(C)=15MONYY**	**(C)=15MONYY**
	Before Treatment Start	Before Treatment Start	Before Treatment Start	Before Treatment Start
YYYY = CFY	**(B)**	**(C)=15MONYY**	**(B)**	**(A)=01MONYYYY**
	Uncertain	Before Treatment Start	Uncertain	After Treatment Start
YYYY > CFY	**(E)= 01JANYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**	**(A)=01MONYYYY**
	After Treatment Start	After Treatment Start	After Treatment Start	After Treatment Start

Before Treatment Start	Partial indicates date prior to Treatment Start Date
After Treatment Start	Partial indicates date after Treatment Start Date
Uncertain	Partial insufficient to determine relationship to Treatment Start Date
LEGEND:	
(A)	MAX(01MONYYYY,TRTSTD+1)
(B)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in(. , 2) THEN TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY
(F)	IF CMDTYP1C IN (1,3) THEN TRTSTD-1 ELSE IF CMDTYP1C in (. , 2) THEN TRTSTD+1

5.1.3.1 Prior therapies date imputation

Not applicable

5.1.3.2 Post therapies date imputation

Not applicable

5.1.3.3 Other imputations

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and above.

5.3 Laboratory parameters derivations

Refer to main section to SAP

5.4 Statistical models

5.4.1 Primary analysis

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, country and stratification factor diagnosis (PsA or axSpA).

```
Proc logistic data=aaa;
Class TRT OCUNTRY STRATA / param=glm;
Model AVAL = TRT COUNTRY STRATA;
Lsmeans TRT / diff cl exp;
Ods output diffs=lsm_diff;
Run;
```

In cases where separation is a concern for the primary endpoint at Week 24, e.g. 0% or 100% response in one treatment (sub)group, an exact logistic regression model will be applied to all visits. To ensure convergence, this model will not include any continuous covariates.

SAS Code for Logistic model:

```
Proc logistic data=aaa exactonly;
Class TRT STRATA / param=glm;
Model AVAL = TRT STRATA;
Exact TRT / estimate=both;
Ods output exactoddsratio=exactoddsratio;
Run;
```

For subgroup analysis, the above code will be used for each stratification factor.

The primary model will also be recalculated with the above factors included as well as with respective tersm for a subgroup*treatment interaction.

5.4.2 Key secondary analysis

Not applicable

5.4.3 Secondary analysis

Categorical variables will be analyses using the logistic model, code is described above.

Endpoints with continuous data type expected to be normally distributed will be analyzed using an analysis of covariance (ANCOVA) model with treatment and baseline stratification factor, country and baseline value as covariate. Confidence intervals for the difference between each dose of secukinumab and placebo will be calculated.

SAS code for ANCOVA:

```
proc mixed data=aaa;
class TRT COUNTRY STRATA;
model response = TRT STRATA COUNTRY BASE / s;
lsmeans TRT / diff;
run;
```

5.5 Rule of exclusion criteria of analysis sets

Table 5.1-4 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01A	ICF is not signed or missing or date of signing ICF is missing	EXCLUDE FROM FAS AND SAF	3
INCL01B	ICF date is after visit or assessment date	INCLUDE IN EVERYTHING	0
INCL02A	Pregnant or lactating female patients	INCLUDE IN EVERYTHING	0
INCL02B	Age is less than 18 years	INCLUDE IN EVERYTHING	0
INCL03A	Diagnosis of PsA classified by CASPAR criteria with no symptoms or symptoms for less than 6 months	INCLUDE IN EVERYTHING	0
INCL03B	Active PsA as not assessed by greater than 1/78 tender joints and greater than 1/76 swollen joints at Baseline.	INCLUDE IN EVERYTHING	0
INCL04A	No objective signs of inflammation at Screening, no evident of Sacroiliac joint inflammation or radiographic sacroilitis and hsCRP less than ULN	INCLUDE IN EVERYTHING	0
INCL04B	Total BASDAI < 4 (0–10) at Baseline	INCLUDE IN EVERYTHING	0
INCL05	Subject with no diagnosis of Achilles tendon enthesitis	INCLUDE IN EVERYTHING	0
INCL06	Onset of heel pain < 1 month or > 5 years at baseline	INCLUDE IN EVERYTHING	0
INCL07	Heel enthesitis is not MRI-positive according to the investigator`s judgement.	INCLUDE IN EVERYTHING	0
INCL08	Subject is intolerable or toxified or contraindicated to NSAIDs standard treatment for heel enthesitis	INCLUDE IN EVERYTHING	0
INCL09	Rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) antibodies is positive at Screening	INCLUDE IN EVERYTHING	0
INCL10A	Subject are inadequate response to NSAIDs at the highest recommended dose at least 1 month prior to randomization to enroll into study.	INCLUDE IN EVERYTHING	0
INCL10B	Subject is inadequate response or failure to respond, or less than 1 month if therapy	INCLUDE IN EVERYTHING	0
INCL11A	Subject is unstable to remain on regular dose of NSAIDs as part of PsA or axSpA therapy for 2 weeks before study randomization	INCLUDE IN EVERYTHING	0
INCL11B	Subject is unable to remain up to Week 24 on stable regular dose of NSAIDs as part of PsA or axSpA therapy	INCLUDE IN EVERYTHING	0
INCL12A	Patient taking corticosteroid is unable to remain on stable dose of less than or equal of 10 mg/day prednisone for 2 weeks before randomization	INCLUDE IN EVERYTHING	0
INCL12B	Patient taking corticosteroid is unable to remain on stable dose up to week 24	INCLUDE IN EVERYTHING	0
INCL13A	Patient taking MTX or axSpA-sulfasalazine is not taken it for atleast 3 months	INCLUDE IN EVERYTHING	0
INCL13B	Patient taking MTX or axSpA-sulfasalazine is unable to remain on stable dose for at least 4 weeks prior to randomization	INCLUDE IN EVERYTHING	0
INCL13C	Patient taking MTX or axSpA-sulfasalazine is unable	INCLUDE IN	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
	to remain on stable dose for up to Week 24	EVERYTHING	
INCL14	Patient is on MTX but not on folic acid supplementation at randomization	INCLUDE IN EVERYTHING	0
INCL15A	Patient who is on DMARD other than MTX or - only in case of axSpA - sulfasalazine is not discontinued the DMARD for 4 weeks prior to randomization.	INCLUDE IN EVERYTHING	0
INCL15B	Patients who are on leflunomide, has not been discontinued for 8 weeks unless a cholestyramine washout has been performed prior to randomization to randomized into study.	INCLUDE IN EVERYTHING	0
INCL16	Patients are not TNFα inhibitor-naïve	INCLUDE IN EVERYTHING	0
EXCL01	Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process	INCLUDE IN EVERYTHING	0
EXCL02	Patient took high potency opioid analgesics (e.g. methadone, hydromorphone, morphine).	INCLUDE IN EVERYTHING	0
EXCL03	Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor	INCLUDE IN EVERYTHING	0
EXCL04	Patient used any of investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug.	INCLUDE IN EVERYTHING	0
EXCL05A	Patient is using Oral or topical retinoids of psoriasis treatments / medications	INCLUDE IN EVERYTHING	0
EXCL05B	Patient is using Photochemotheraphy of psoriasis treatments / medications and not undergone 4 weeks of washout treatment	INCLUDE IN EVERYTHING	0
EXCL05C	Patient is using Phototheraphy of psoriasis treatments / medications and not undergone 2 weeks of washout treatment	INCLUDE IN EVERYTHING	0
EXCL05D	Patient is using Topical skin treatments of psoriasis treatments / medications and not undergone 2 weeks of washout treatment	INCLUDE IN EVERYTHING	0
EXCL06	History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes	INCLUDE IN EVERYTHING	0
EXCL07	Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization	INCLUDE IN EVERYTHING	0
EXCL08	Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization.	INCLUDE IN EVERYTHING	0
EXCL09	Patients previously have been treated with TNF inhibitors	INCLUDE IN EVERYTHING	0
EXCL10	Patients have received biologic immunomodulating agents	INCLUDE IN EVERYTHING	0
EXCL11	Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents	INCLUDE IN EVERYTHING	0
EXCL12	Pregnant or nursing (lactating) women, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test	INCLUDE IN EVERYTHING	0
EXCL13	Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception before 3 months during dosing of study treatment	INCLUDE IN EVERYTHING	0
EXCL14	Active ongoing inflammatory diseases or including	INCLUDE IN	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
	inflammatory bowel disease or uveitis.	EVERYTHING	
EXCL15	Patient unacceptable risk for participation in the opinion of the investigator fior underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions in the opinion of the investigator	INCLUDE IN EVERYTHING	0
EXCL16	Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension or congestive heart failure or uncontrolled diabetes.	INCLUDE IN EVERYTHING	0
EXCL17A	Any single parameter (AST/SGOT, ALT/SGPT, alkaline phosphatase) exceeded 2 × ULN.	INCLUDE IN EVERYTHING	0
EXCL17B	Total bilirubin concentration is increased above 2 × ULN and serum bilirubin exceeding the value of 1.6 mg/dL (27 µmol/L).	INCLUDE IN EVERYTHING	0
EXCL18	History of renal trauma, glomerulonephritis, or patients with 1 kidney only, or a serum creatinine level exceeding 1.5 mg per dL	INCLUDE IN EVERYTHING	0
EXCL19	Screening total white blood cell (WBC) count less than 3000/µL, or platelets less than 100000/µL or neutrophils less than 1,500/µL or hemoglobin less than 8.5 g per dL (85 g per L).	INCLUDE IN EVERYTHING	0
EXCL20	Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization.	INCLUDE IN EVERYTHING	0
EXCL21	Patient is having history of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection	INCLUDE IN EVERYTHING	0
EXCL22	Known infection with human immunodeficiency virus (HIV) or hepatitis B or hepatitis C at screening or randomization	INCLUDE IN EVERYTHING	0
EXCL23	History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years.	INCLUDE IN EVERYTHING	0
EXCL24	Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial	INCLUDE IN EVERYTHING	0
EXCL25	Inability or unwillingness to undergo repeated venipuncture	INCLUDE IN EVERYTHING	0
EXCL26	Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.	INCLUDE IN EVERYTHING	0
EXCL27	Donation or loss of 400 mL or more of blood within 8 weeks before randomization	INCLUDE IN EVERYTHING	0
EXCL28	History or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization.	INCLUDE IN EVERYTHING	0
EXCL29	Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.	INCLUDE IN EVERYTHING	0
WITH01	Patient becomes pregnant, while taking study medication.	INCLUDE IN EVERYTHING	0
OTH01	Pregnancy test not performed as required per protocol	INCLUDE IN EVERYTHING	0
OTH02	Pregnancy not reported within 24 hrs to Novartis while patient is on study treatment	INCLUDE IN EVERYTHING	0
WITH02	ICF withdrawn but patient continuing in the study	INCLUDE IN EVERYTHING (Delete	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
		post withdrawal data)	
WITH03	Pregnant patient not withdrawn from study	INCLUDE IN EVERYTHING	0
WITH04	Pregnant patient not withdrawn from study as local workup cannot exclude definite pregancy	INCLUDE IN EVERYTHING	0
TRT01	Dosing error in comparative dosing phase	INCLUDE IN EVERYTHING	0
OTH03	Rescue medication used	INCLUDE IN EVERYTHING	0
COMD01	Prohibited medication consumed during study or washout period not observed.	INCLUDE IN EVERYTHING	0
EXCL30	Inability or unwillingness to undergo MRI of the feet preceding but enrolled in study	INCLUDE IN EVERYTHING	0
OTH04	Leeds Enthesitis Index assesment is missing but treatment period 1 completed	INCLUDE IN EVERYTHING	0

Table 5.1-5 Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3, 6
FAS	1, 3

Table 5.1-6 Population code text

Population Code	Population code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF

6 Reference

Not applicable