Clinical Development

AIN457/Secukinumab

CAIN457F3302 / NCT02721966

MAXIMISE (Managing AXIal Manifestations in PsorIatic Arthritis with SEcukinumab), a randomized, double-blind, placebo-controlled, multicenter, 52-week study to assess the efficacy and safety of secukinumab 150 mg or 300 mg s.c. in patients with active psoriatic arthritis and axial skeleton involvement who have inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs)

Statistical Analysis Plan (SAP)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
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
ATC	Anatomical Therapeutic Classification
AxPsA	Axial psoriatic arthritis (i.e. psoriatic arthritis with axial involvement)
BASDAI	Bath ankylosing spondylitis disease activity index
BCC	Basal cell carcinoma
BMI	Body mass index
Bpm	Beats per minute
CASPAR	Classification criteria for psoriatic arthritis
CI	Confidence interval
CMD	Concomitant medication
CRF	Case Report Form
CRO	Clinical research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug administration record
DMARD	Disease-modifying anti-rheumatic drug
DVU	Disc Vertrebral Unit
ECG	Electrocardiogram
FACIT-Fatigue©	Functional assessment of chronic illness therapy fatigue scale
FAS	Full Analysis Set
GGT/γGT	Gamma glutamyl transferase
HAQ-DI©	Health assessment questionnaire – disability index
HDL	High density lipoprotein
HGB	Hemoglobine
HR-QoL	Health-related quality of life
ICF	Informed consent form
IL	Interleukin
IRT	Interactive response technology
i.v.	Intravenous(ly)
LDL	Low density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LOCF	Last observation carried forward

MedDRA	Medical Dictionary for Drug Regulatory Affairs
MRMM	Mixed-effects repeated measures model
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTX	Methotrexate
NMQ	Novartis MedDRA Queries
NSAID	Non-steroidal anti-inflammatory drug
PD	Protocol Deviation
PFS	Prefilled syringe
PsA	Psoriatic arthritis
PPS	Per-protocol set
PSOC	Primary system organ class
PT	Preferred term
QFT	QuantiFERON tuberculosis gold test
RAN	Randomized set
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SCC	Squamous cell carcinoma
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SPARCC	Spondyloarthritis Research Consortium of Canada
SPP	Safety Profiling-Plan
TB	Tuberculosis
TBL	Total bilirubine
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cells

1 Introduction

This document describes the planned statistical methods for all safety and efficacy analyses, which will be used in the phase IIIb clinical trial AIN457F3302.

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 using statistical software SAS version 9.4 according to the data analysis section 9 of the study protocol, which is available in Appendix 16.1.1 of the CSR. 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 16.1.9 of CSR.

Please refer to the following document:

Clinical Protocol CAIN457F3302

1.1 Study design

This is a 52-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter study to assess the efficacy of secukinumab 150 mg or 300 mg in patients with AxPsA who have had an inadequate response to two different NSAIDs. The study will consist of two treatment periods; a double-blind placebo-controlled period from Baseline to Week 12 followed by a double-blind secukinumab treatment period from Week 12 to Week 52.

The schematic of study design is given in Figure 1.1 below.

Planned number of patients and randomization

A total of 495 patients (165 patients per group) will be recruited to compensate dropouts and protocol violators.

Patient eligibility will be assessed during a maximum screening period of 8-weeks. At Baseline, all patients whose eligibility is confirmed will be randomized in a 1:1:1 ratio to secukinumab 150 mg, secukinumab 300 mg or placebo. At Week 12, patients randomized to placebo at Baseline will be re-randomized (1:1) to active treatment with secukinumab 150 mg or secukinumab 300 mg.

Group 1: secukinumab 150 mg

Treatment Period 1

secukinumab 150 mg (1 × 1.0 mL prefilled syringes (PFS)) + placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

Group 2: secukinumab 300 mg

Treatment Period 1

secukinumab 300 mg (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

Group 3: placebo

Treatment Period 1

placebo (2 × 1.0 mL PFS) administered at Baseline, Week 1, 2, 3 and 4, then 4 weeks later at Week 8.

Treatment Period 2

secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48), OR

secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 12 to Week 52 (last dose on Week 48).

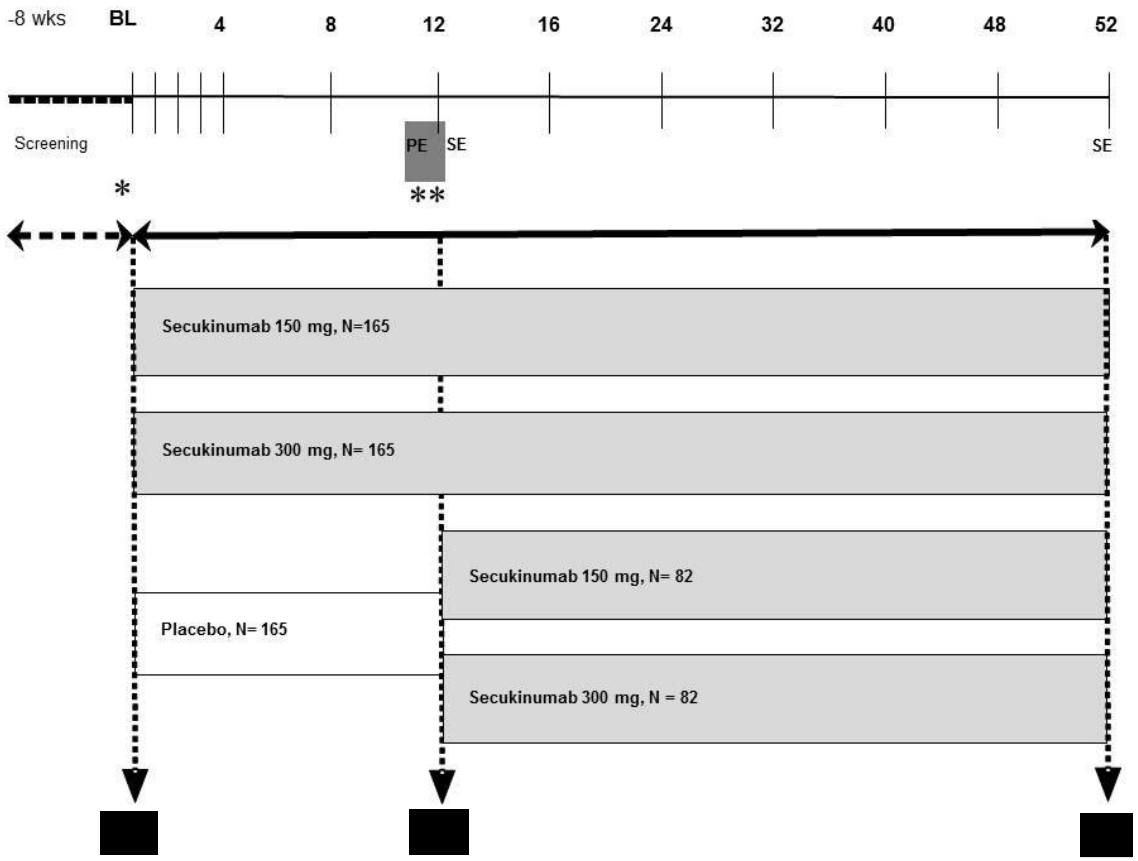
Patients, investigator staff, persons performing the assessments and data analysts will remain blinded to the identity of the treatment from the time of randomization until database lock. No stratification at randomization will be performed.

Primary analysis time point

The primary and key secondary analyses will be performed at Week 12.

[redacted]

Figure 1.1: Study Design



* Randomization

** RE-randomization for placebo group

[redacted], PE = primary endpoint, SE = Secondary endpoints

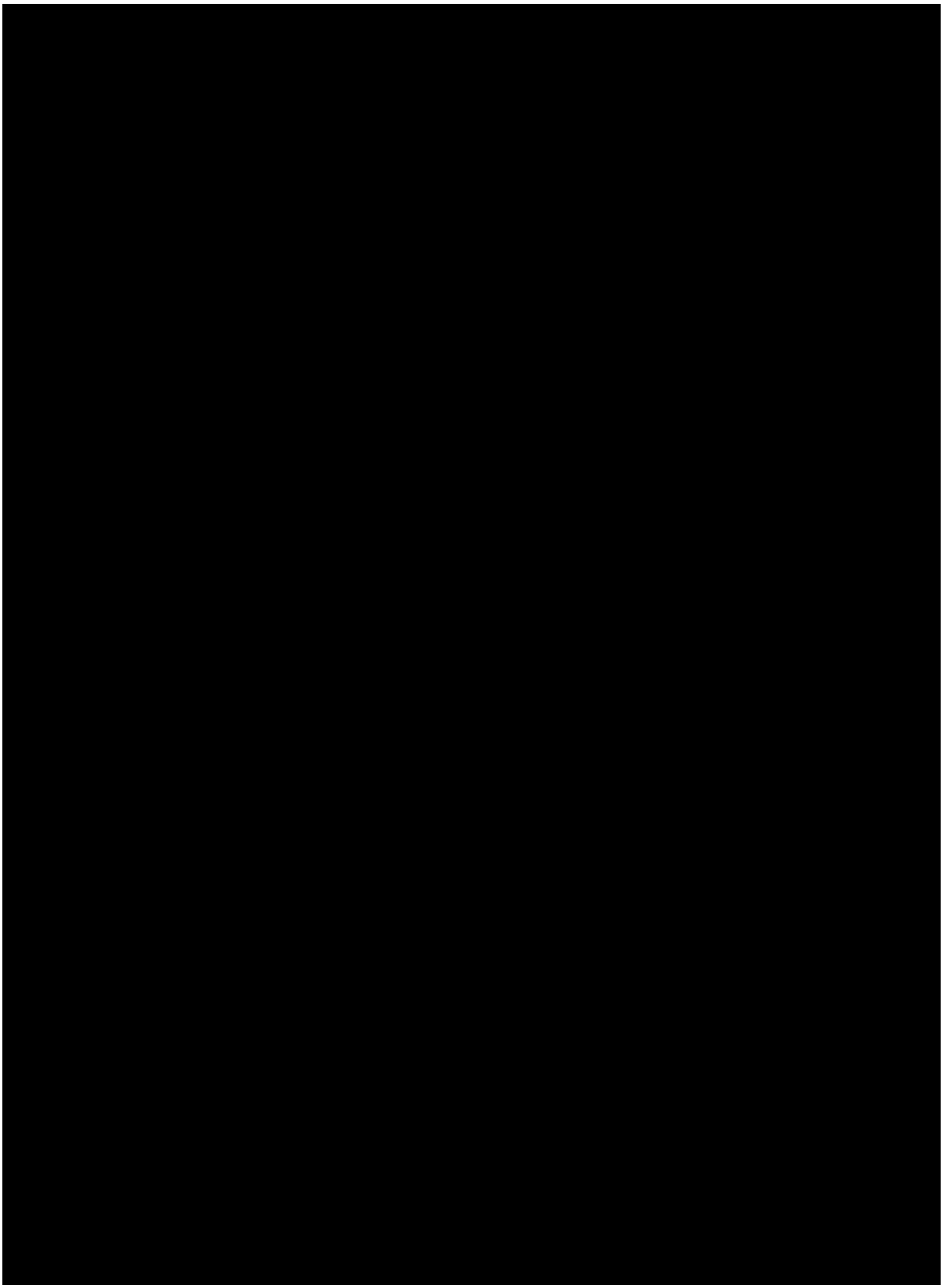
1.2 Study objectives and endpoints

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	
To demonstrate that secukinumab 300 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12.	Proportion of patients with ASAS 20 response at Week 12
Key secondary objective	
To demonstrate that secukinumab 150 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12 after superiority of 300 mg is established	Proportion of patients with ASAS 20 response at Week 12, after superiority of 300 mg is established

Secondary objectives	
To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12	Proportion of patients with ASAS 40 response at Week 12
To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of ASAS 40 at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo in the achievement of BASDAI 50 at Week 12	Proportion of patients with BASDAI 50 response at Week 12
To evaluate secukinumab 150 mg s.c. versus placebo in the achievement of BASDAI 50 at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo in the reduction of spinal pain measured by visual analog scale (VAS) at Week 12	Mean change from baseline of spinal pain assessed by VAS at Week 12
To evaluate secukinumab 150 mg s.c. versus placebo in the reduction of spinal pain measured by VAS at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index at Week 12	Mean change from baseline of SPARCC enthesitis index at Week 12.
To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in SPARCC enthesitis index at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in health assessment questionnaire disability index (HAQ-DI©) at Week 12	Mean change from baseline of health assessment questionnaire disability index (HAQ-DI©) at Week 12.
To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in HAQ-DI© at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©) at Week 12	Mean change from baseline of functional assessment of chronic illness therapy fatigue scale (FACIT-Fatigue©) at Week 12
To evaluate secukinumab 150 mg versus placebo in achieving an improvement in the FACIT-Fatigue© at Week 12	

To evaluate secukinumab 300 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12	Mean change from baseline of ASAS health index at Week 12
To evaluate secukinumab 150 mg s.c. versus placebo in achieving an improvement in the ASAS health index at Week 12	
To evaluate secukinumab 300 mg s.c. versus placebo based on the proportion of patients achieving an ACR 20 response at Week 12	Proportion of patients with ACR 20 response at Week 12
To evaluate secukinumab 150 mg s.c. versus placebo based on the proportion of patients achieving an ACR 20 response at Week 12	
To evaluate the 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 data will be analyzed by Novartis and/or by the designated CRO. It is planned that the data from all centers that participate in this protocol will be used for analysis. 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).

As the primary endpoint analysis will be performed at Week 12, there will be a database freeze after all patients have completed Week 12 assessments. A selected Novartis clinical team will be unblinded to the Week 12 results. Summary results may be shared internally and externally; however, individual unblinded patient data will not be disclosed. A final database lock will occur when all patients have completed the study.

Summary statistics for continuous variables will include number of patients (N), mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in the number and percent of patients in each category. Summary statistics will also be presented graphically wherever applicable.

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

Data analyses will be presented by treatment group. Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by the following 3 treatment groups. Patients may be included in more than one treatment group for some analyses (e.g. exposure-adjusted adverse events over the entire treatment period).

Eligible patients will be randomized to secukinumab 150 mg (Group 1), secukinumab 300 mg (Group 2) or placebo (Group 3) for the first 12 weeks. Note that the treatment groups for a patient may differ depending on the time period of the analysis and whether one assesses the patient for efficacy or safety.

The analysis will be conducted on all patients' data at Week 12 and at the time, the trial ends (Week 52).

Comparative efficacy data

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo) will focus on the time period when both active drug and the placebo are given in a manner suitable for making comparisons (i.e., first 12-weeks of treatment). Comparative efficacy will be performed based on the FAS population using the randomized treatment. After week 12 till week 52, the efficacy endpoints will be summarized descriptively or otherwise specified using inferential analysis, on the FAS population.

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 2 treatment periods for this study defined as:

Treatment Period 1 is defined as a 12 Week placebo-controlled, double-blind treatment period starting from baseline till Week 12.

Treatment Period 2 is a 40 Week double-blinded active treatment period starting from Week 12 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 this study, the treatment phase consists of 52 weeks (for treatment group 1 or group 2) for secukinumab, and 12 weeks of on-treatment period for placebo and 40 weeks of on treatment for secukinumab (for treatment group 3).

2.1.2 Visits windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. The visit windows are shown in Table 2-1. These 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 46 instead of on Day 29, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

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

Table 2-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 1	1	8	Day 2-11
Week 2	2	15	Day 12-18
Week 3	3	22	Day 19-25
Week 4	4	29	Day 26-43
Week 8	8	57	Day 44-71
Week 12	12	85	Day 72-104
Week 16	16	113	Day 105-141
Week 24	24	162	Day 142-183
Week 32	32	218	Day 184-253
Week 40	40	289	Day 254-323
Week 48	48	337	Day 324-351
Week 52	52	365	Day 352 onwards

* Baseline measurement before the first drug administration for safety assessments and before the randomization for efficacy assessments. For efficacy visit windows, refer to date of randomization.

For parameters, which are not collected at every visit (e.g., FACIT-Fatigue©, HAQ-DI©), visit windows defined in Table 2-4 will be combined. For example, if a parameter is measured at Week 12 and Week 24 only, Week 12 visit window will extend from Day 2 to Day 104 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 105 to Day 183 (combining Week 16 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.1.3 below are applied.

Table 2-4a Drug administration windows for scheduled visits of Exposure Data

The administration of study drug at weeks 20, 28, 36, and 44 is not in relation to a study visit. For exposure data, a specific assessment window for those weeks is used in order to account for the home administrations at those weeks.

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

[redacted]

2.1.3 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 2.1.1. For post-baseline visit windows, the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined.
- in case qualitative variables are based on quantitative variables, e.g. ACR 20 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

Timing of measurement	Type of data	Rule
Baseline	All data	The last non-missing measurement made prior to or on the date of administration of the first dose of study treatment (the reference start date / Day 1). If a patient did not receive any dose of study treatment, then the randomization date will be used. Only date part is considered if just one assessment on Day 1. If there are multiple assessments on Day 1, following rules will apply: a. If assessment time exists, • select the last available measurement prior to reference start date/time considering time; • if no measurement prior to reference start date/time considering time, select the earliest measurement post reference start date/time considering time. b. If assessment time does not exist, select the available measurement from the lowest CRF visit number.

Timing of measurement	Type of data	Rule
Post-baseline efficacy	All data	The measurement closest to the target day will be used. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used. Cases where the same parameter is recorded more than once on the same date will be handled as follows: • If time of completion exists, the earliest measurement will be used; • If time does not exist, the measurement from the lowest CRF visit number will be used.

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, mis-randomized patients (mis-randomized in IRT) will be excluded from the randomized set.

Mis-randomized patients are defined as those patients, who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized patients are treated as screen failures.

Any in-eligible patient, who has been randomized and treated during the study, should be part of Randomized Set and Safety Set but excluded from FAS.

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.

[redacted]

Per-protocol set: This set includes all patients, who completed the study without a major protocol deviation.

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

There is no planned subgroup of interest.

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 screened will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of patients in the randomized set who enrolled, and who completed the treatment period and who discontinued the study prematurely (including the primary reason for discontinuation) will be presented at the end of each treatment period (Week 12 and Week 52), if appropriate, for each treatment group and all patients.

The number and percentage of patients who took rescue medication and hence discontinued at week 12 and week 52 will be presented. For each protocol deviation (PD), the number and percentage of patients for whom the PD applies will be tabulated.

PDs will be assigned to TP1 and TP2 based upon the starting dates. These dates are not part of the clinical database, therefore they will be provided by the clinical team in a separate file to the statistical team for analysis.

2.3.2 Patient demographic and other baseline characteristics

The following demographic and baseline variables, if collected, will be summarized:

Continuous variables:

- Age (which is derived from date/year of birth and the screening assessment date)
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2
- For BMI, height and body weight used is the last value prior to randomization. If there is no weight recorded prior to taking of study drug, BMI will be missing.

Categorical variables:

- Age categories (<65 years, ≥65-<75years, 75 years and older; <45 and >=45 years for final analysis)

  For final analysis, age groups will be redefined as <45 years, 45 years and older.
- Sex

- Race
- Ethnicity
- Child-bearing potential (for females only)
- Smoking status at baseline
- Source of patient referral

Baseline disease characteristics will also be summarized for the following variables, in two separate tables:

- History of AxPsA including time (years) since first diagnosis of AxPsA, time since first signs and symptoms, previous treatments of AxPsA and reasons for discontinuation of these treatments.
- CASPAR criteria, Patient's global assessment of disease activity and other ASAS components, SPARCC, ACR components, [redacted] HAQ-DI©, FACIT-Fatigue©, ASAS health index, Spinal pain VAS.

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.

Disease severity at baseline will be defined based upon BASDAI score at baseline as following:

- Group 1: 4 <= BASDAI <= 6.5
- Group 2: 6.5 < BASDAI <= 8.5
- Group 3: BASDAI >8.5

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 and medical history will be provided as well. Smoking history (baseline) will be summarized and listed. 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 summaries by treatment will be performed by the actual treatment received (as follows) or treatment sequence for each treatment period.

Randomized treatment:

- AIN457 300 mg
- AIN457 150 mg
- Placebo

Treatment sequence:

- AIN457 300 mg
- AIN457 150 mg
- Placebo to AIN457 300 mg
- Placebo to AIN457 150 mg

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 up to Week 12 and Week 52.

Duration of exposure

The duration of exposure to study treatment will also 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 for secukinumab groups will be defined as the time from first dose of study treatment to the time of treatment end for each treatment period. Duration of exposure for the placebo group will be defined as the time from first dose of placebo treatment to the time of treatment end in treatment period 1 and the time from first dose of active treatment to the time of treatment end in treatment period 2.

For patients who discontinue, this will be the patient's last visit in the corresponding treatment period.

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

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

The analyses of duration of exposure described above will be done for the entire study treatment periods.

Compliance

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

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 PsA 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 PsA therapies previously.

In addition to that, summary of doses will also be performed for NSAID, MTX and corticosteroids. Comparison of median dose with ASAS recommendations will also be summarized.

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 benefit or worsening of disease, if rescue with prohibited treatments occurs prior to completion of Week 52 assessments, patients can be discontinued from the study treatment (as per the CTT's discretion) but can continue with the study visit assessments until at least Week 12.

Rescue medication will be summarized similarly to concomitant medication.

2.5 Analysis of the primary objective

The primary objective is to demonstrate that efficacy of secukinumab 300 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12.

2.5.1 Primary endpoint

The primary efficacy endpoint is the proportion of patients with ASAS 20 response in secukinumab 300 mg s.c. and placebo at Week 12. The total spinal pain will be used for the calculation of the ASAS response.

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

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the Secukinumab 300 mg treatment group versus placebo group.

Let p_0 denotes the proportion of ASAS 20 responders at Week 12 for placebo group and p_1 denotes the proportion in secukinumab 300 mg treatment group.

In statistical terms, the following hypothesis will be tested:

H_1: $p_1 = p_0$, versus H_{A1}: $p_1 \neq p_0$

In other words,

H_1: Secukinumab 300 mg treatment group is not different to placebo group with respect to ASAS 20 response at Week 12

The primary analyses will be conducted via logistic regression with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab 300 mg treatment group to placebo group at Week 12.

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

Summary statistics will also be reported for each treatment group, concomitant MTX intake status and by visit. Graphical representation will also be performed.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS 20 response for data up to Week 12 will be handled by multiple imputations technique.

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

2.6 Analysis of the key secondary objective

The key secondary objective is to demonstrate that efficacy of secukinumab 150 mg s.c. is superior to placebo in the achievement of ASAS 20 response at Week 12, after primary objective is met i.e., after superiority is demonstrated for secukinumab 300 mg to placebo at Week 12.

2.6.1 Key secondary endpoint

The key secondary efficacy endpoint is the proportion of patients with ASAS 20 response in secukinumab 150 mg s.c. and placebo at Week 12.

The key secondary analyses will only be performed if superiority is demonstrated for secukinumab 300 mg to placebo at Week 12. The analysis of the key secondary variable will be based on the FAS.

2.6.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the Secukinumab 150 mg treatment group versus placebo group, after superiority is demonstrated for secukinumab 300 mg to placebo at Week 12.

Let p_0 denotes the proportion of ASAS 20 responders at Week 12 for placebo group and p_2 denotes the proportion in secukinumab 150 mg treatment group.

If primary objective (superiority of secukinumab 300mg to placebo) is met, the following hypothesis will be tested:

H_2: $p_2 = p_0$, versus H_{A2}: $p_2 \neq p_0$

In other words,

H_2: Secukinumab 150 mg treatment group is not different to placebo group with respect to ASAS 20 response at Week 12

The key secondary analyses will be conducted analogous to the primary analyses, i.e., via logistic regression with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab 150 mg treatment group to placebo group at Week 12.

Summary statistics will also be reported for each treatment group and by visit. Graphical representation will also be performed.

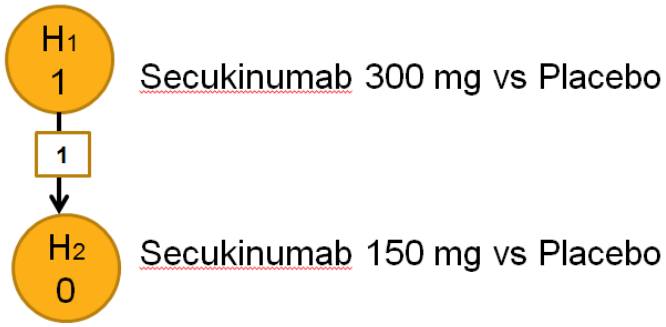
Testing strategy

The family-wise error will be set to α=5% (2-sided). H_1 is tested at α (2-sided). The graphical approach of Bretz (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the hierarchical testing strategy (**Error! Reference source not found.**).

The following hypothesis will be tested sequentially and are included in the hierarchical testing strategy and type-I-error will be set such that a family-wise type-I-error of 5% is kept:

The testing sequence will continue to H_2 at α (2-sided) only if H_1 has been rejected.

Figure 2.6-1: Testing Strategy



Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however, the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS 20 response for data up to Week 12 will be handled by multiple imputation technique as defined in Section 2.5.3.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1.2-1 of Section 1 for the list of secondary objectives.

2.7.1 Secondary endpoints

All the secondary efficacy evaluation will be performed on FAS population.

Refer to Table 1.2-1 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 secondary variables. All secondary endpoints will be tested exploratively outside the confirmatory framework:

- H_{3a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ASAS 40 response at Week 12
- H_{3b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ASAS 40 response at Week 12
- H_{4a}: secukinumab 300 mg treatment group is not different to placebo group with respect to BASDAI 50 response at Week 12
- H_{4b}: secukinumab 150 mg treatment group is not different to placebo group with respect to BASDAI 50 response at Week 12
- H_{5a}: secukinumab 300 mg treatment group is not different to placebo group with respect to spinal pain (VAS) response at Week 12
- H_{5b}: secukinumab 150 mg treatment group is not different to placebo group with respect to spinal pain (VAS) response at Week 12
- H_{6a}: secukinumab 300 mg treatment group is not different to placebo group with respect to SPARCC enthesitis index at Week 12
- H_{6b}: secukinumab 150 mg treatment group is not different to placebo group with respect to SPARCC enthesitis index at Week 12
- H_{7a}: secukinumab 300 mg treatment group is not different to placebo group with respect to HAQ-DI© at Week 12
- H_{7b}: secukinumab 150 mg treatment group is not different to placebo group with respect to HAQ-DI© at Week 12
- H_{8a}: secukinumab 300 mg treatment group is not different to placebo group with respect to FACIT-Fatigue© score at Week 12
- H_{8b}: secukinumab 150 mg treatment group is not different to placebo group with respect to FACIT-Fatigue© score at Week 12
- H_{9a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ASAS Health index at Week 12
- H_{9b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ASAS Health index at Week 12
- H_{10a}: secukinumab 300 mg treatment group is not different to placebo group with respect to ACR 20 response at Week 12
- H_{10b}: secukinumab 150 mg treatment group is not different to placebo group with respect to ACR 20 response at Week 12

Analysis of secondary endpoints:

- **ASAS 40 at Week 12**

Response to ASAS 40 at Week 12 will be analyzed using a logistic regression model with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo.

- **BASDAI 50 at Week 12**

BASDAI 50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the Baseline total BASDAI score.

Response to BASDAI 50 at Week 12 will be analyzed using a logistic regression model with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo.

- **Spinal pain (VAS) at Week 12**

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain.

The mean change from baseline of spinal pain at Week 12 will be analyzed by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline measurement in VAS as continuous covariate. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

- **SPARCC enthesitis index at Week 12**

The SPARCC enthesitis index focuses on the clinical evaluation and validation of 16 defined sites.

The mean change from baseline of SPARCC enthesitis index at Week 12 will be analyzed by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline SPARCC index as continuous covariate. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

- **Physical function index (HAQ-DI©) at Week 12**

Refer to Section 2.11

- **FACIT-Fatigue© score at Week 12**

Refer to Section 2.11

- **ASAS Health Index at Week 12**

Refer to Section 2.11

- **ACR 20 response at Week 12**

Response to ACR 20 at Week 12 will be analyzed using a logistic regression model with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab to placebo.

Summary statistics will include relative and absolute frequencies for the binary variable (ASAS 40, BASDAI 50 and ACR 20) and the number of patients (N), minimum, mean, median and maximum for the continuous variable (VAS, SPARCC, etc.,) for each treatment group and by visit. Graphical representation will also be performed.

2.7.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS 40, BASDAI 50 and ACR 20 for data up to Week 12 will be handled by multiple imputations.

Continuous variables (Spinal pain (VAS), SPARCC enthesitis index, HAQ-DI©, FACIT--Fatigue© score and ASAS Health index) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random assumption. For analyses of these parameters, if all post-Baseline values are missing then these missing values will not be imputed and this patient will be removed from the analysis of the corresponding variable, i.e. it might be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

2.8 Safety analyses

All the safety analysis will be performed on the Safety set.

Summaries may be performed separately for the initial (Week 1-12) and entire treatment periods.
The analyses of the follow-up period will be limited to summaries for treatment-emergent adverse events, and serious adverse events.

Safety analyses will be performed 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 did not receive the randomized treatment, 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 and also the relationship with study drug.

2.8.1 Adverse events (AEs)

The crude rates 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, and events until 12 weeks after last dose of study treatment) will be summarized by primary system organ class and preferred term.

In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided for the entire treatment period to adjust for differences in exposure. A graphical display of the crude rates and exposure-adjusted incidence rates will be presented for all AEs and serious AEs by system organ class.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries (crude rates 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 greatest 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 of special interest

Adverse events will also be reported separately by SMQ according to MedDRA, using a narrow search. The MedDRA version used for reporting the study will be described in a footnote.

Follow-up period summaries will be done for all patients in follow-up.

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

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

Algorithms for date imputations will be provided in Programming Specifications.

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

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

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

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by system organ class and preferred term.

2.8.1.1 Adverse events of special interest (AESIs)

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.

To this end, the following events will be considered as adverse events of special interest:

- Major adverse cardiovascular events (MACE): identified per Novartis MedDra Query (NMQ) “MACE (MI, Stroke, Cardiovascular death)”
- Inflammatory bowel disease: identified per NMQ “Inflammatory bowel disease”
- Infections and infestations: identified per SOC “Infections and infestations”
- Malignancy: identified per NMQ “Malignant or unspecified tumors (excluding BCC and SCC)”
- Hypersensitivity and injection site reaction: identified per SMQ “Hypersensitivity”

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

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

Adverse events of special interest analysis will be performed using the time to event analysis, the number of patients with an event, number of patients remaining at risk in the treatment group, estimate of the event rate and its estimated standard error, as estimable, will be provided for each treatment group. Median time to event and quartiles including 95% confidence intervals will be provided. The Kaplan-Meier estimates of the cumulative rate for each treatment group will be plotted.

2.8.2 Deaths

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

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

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, chemistry and urinalysis). In addition to the individual laboratory parameters the ratios “total cholesterol / HDL” and “apolipoprotein B / apolipoprotein A1” will be derived and summarized.

For urinalysis, frequency tables will be presented.

Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test 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

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 patient’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. Also the shifts to the most extreme laboratory test value within a treatment period 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: 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), glucose, cholesterol, triglycerides (TG).

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

Table 2.8-1 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 below:

Table 2.8-2 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:
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.

Separate summaries and listings will be provided for urine pregnancy results by visit for each treatment period.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The following quantitative variables will be summarized: RR interval, PR interval, QRS duration, QT interval, and Fridericia (QTcF) correction will be presented for QTc.

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

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

Summary statistics will be presented for ECG variables by visit and treatment group. In addition, shift tables comparing baseline ECG 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 signs 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 2.8-3 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

An overview of the safety analyses is described in Table 2.8-1 below.

Table 2.8-4 Overview of analyses on some safety endpoints

Analysis period	SAEs	AEs	Study drug related AEs	AESI	Notables for vitals/ECG/ lab criteria
Day 1 – Week 12	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates
Entire Treatment (upto Week 52)	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates	• Crude rates • Exposure time adjusted incidence rates*	• Crude rates

*Exposure time adjusted incidence rates will be done for the following:
• at the PSOC level for all SAEs and all AEs
• at the preferred term level for
  - all SAEs and AESIs

- the common AEs, which are 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

2.9 Pharmacokinetic endpoints

Not Applicable.

2.10 PD and PK/PD analyses

Not Applicable.

2.11 Patient-reported outcomes

Variables related to health-related quality of life (HR-QoL) are described below. All HR-QoL variables will be evaluated based on FAS patients.

Physical function index (HAQ-DI©)

The mean change from baseline of Physical function index (HAQ-DI©) at Week 12 will be analyzed by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline HAQ-DI index as continuous covariate. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

FACIT-Fatigue© score

The mean change from baseline of FACIT-Fatigue© total score at Week 12 will be analyzed by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline FACIT-Fatigue score as continuous covariate. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

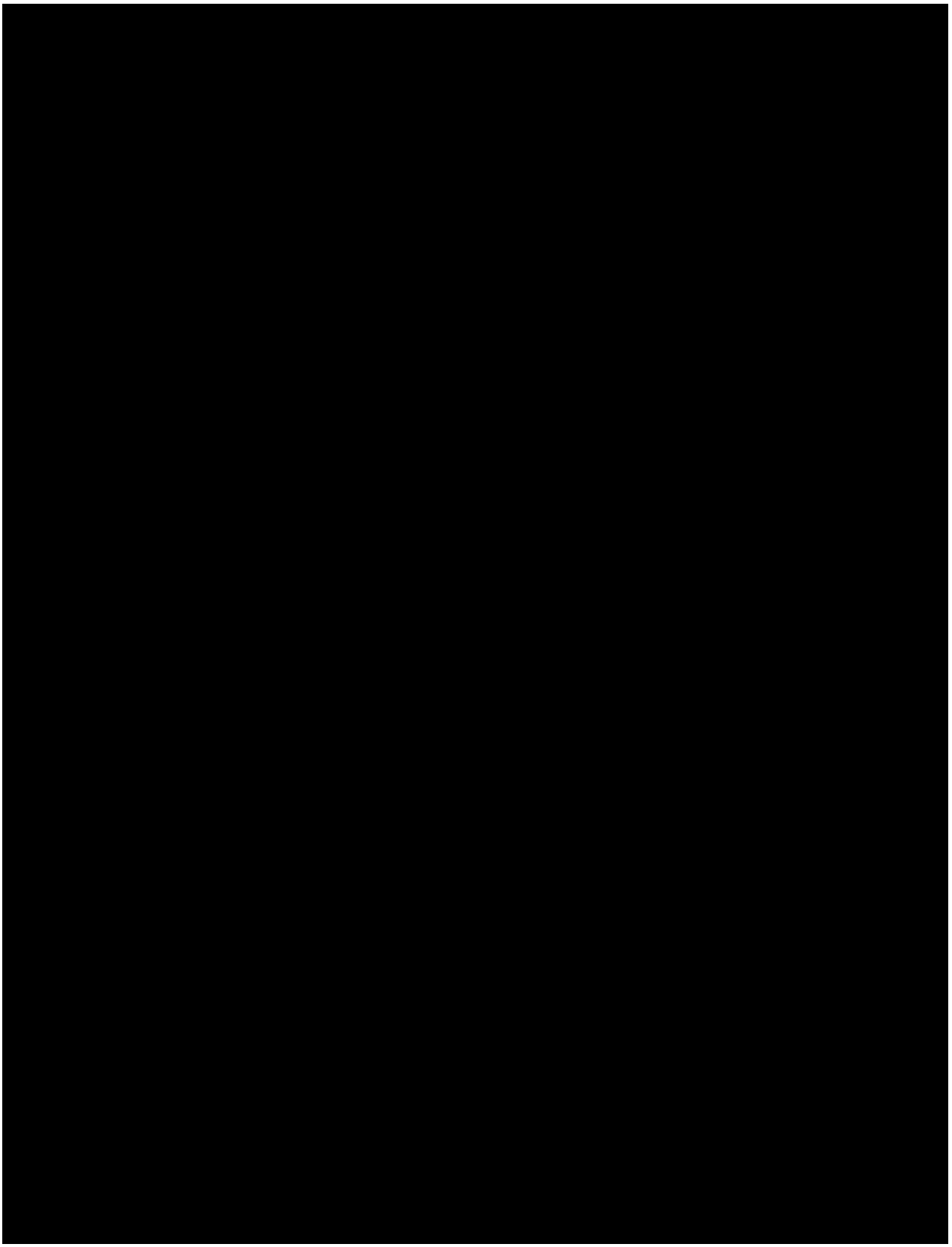
ASAS Health Index

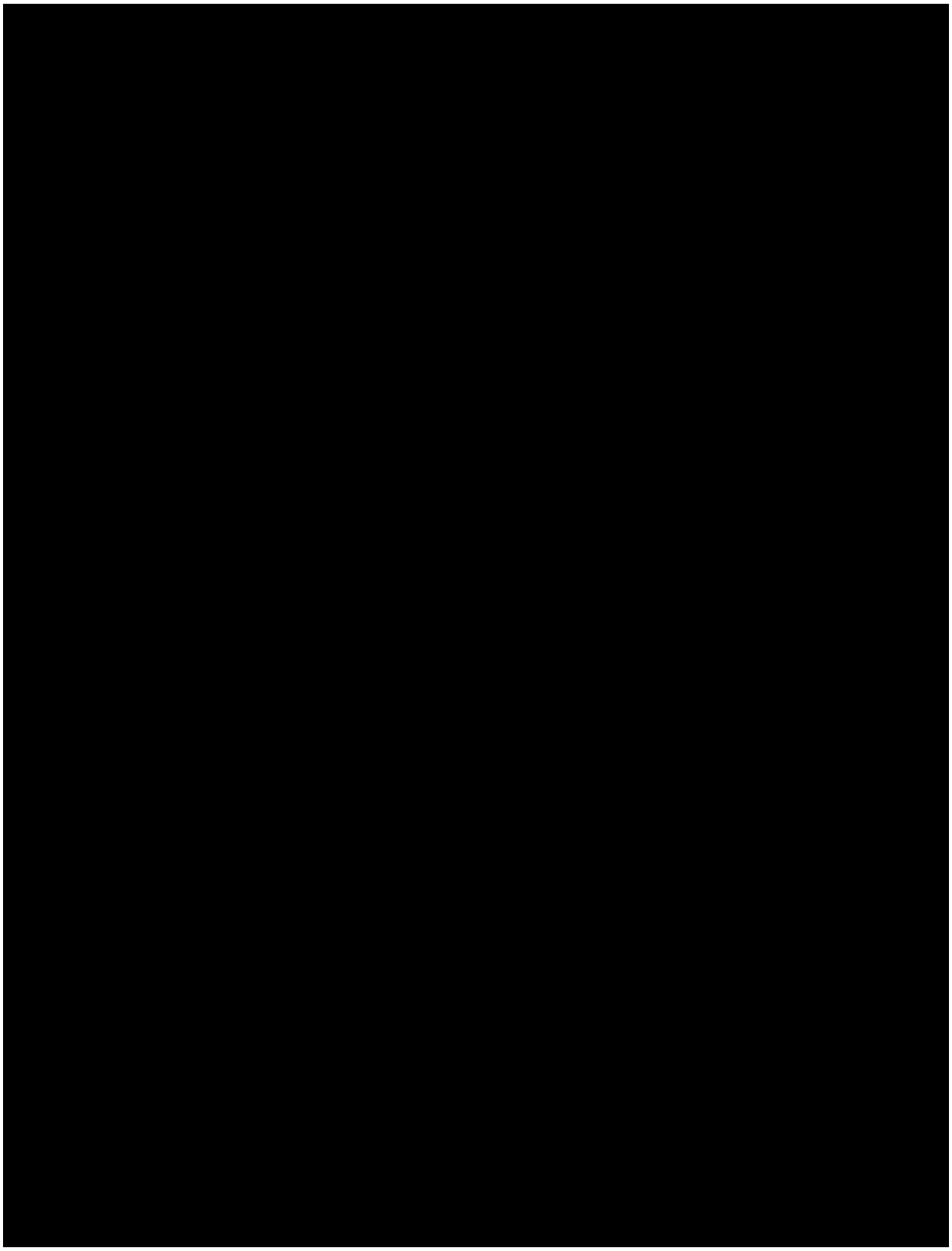
The mean change from baseline of ASAS health index at Week 12 will be analyzed by using an ANCOVA model with treatment group, visit and concomitant MTX intake status, as factors and baseline ASAS Health Index as continuous covariate. The adjusted (LS) mean difference will be calculated as a point estimate together with the corresponding 95% confidence interval and p-value.

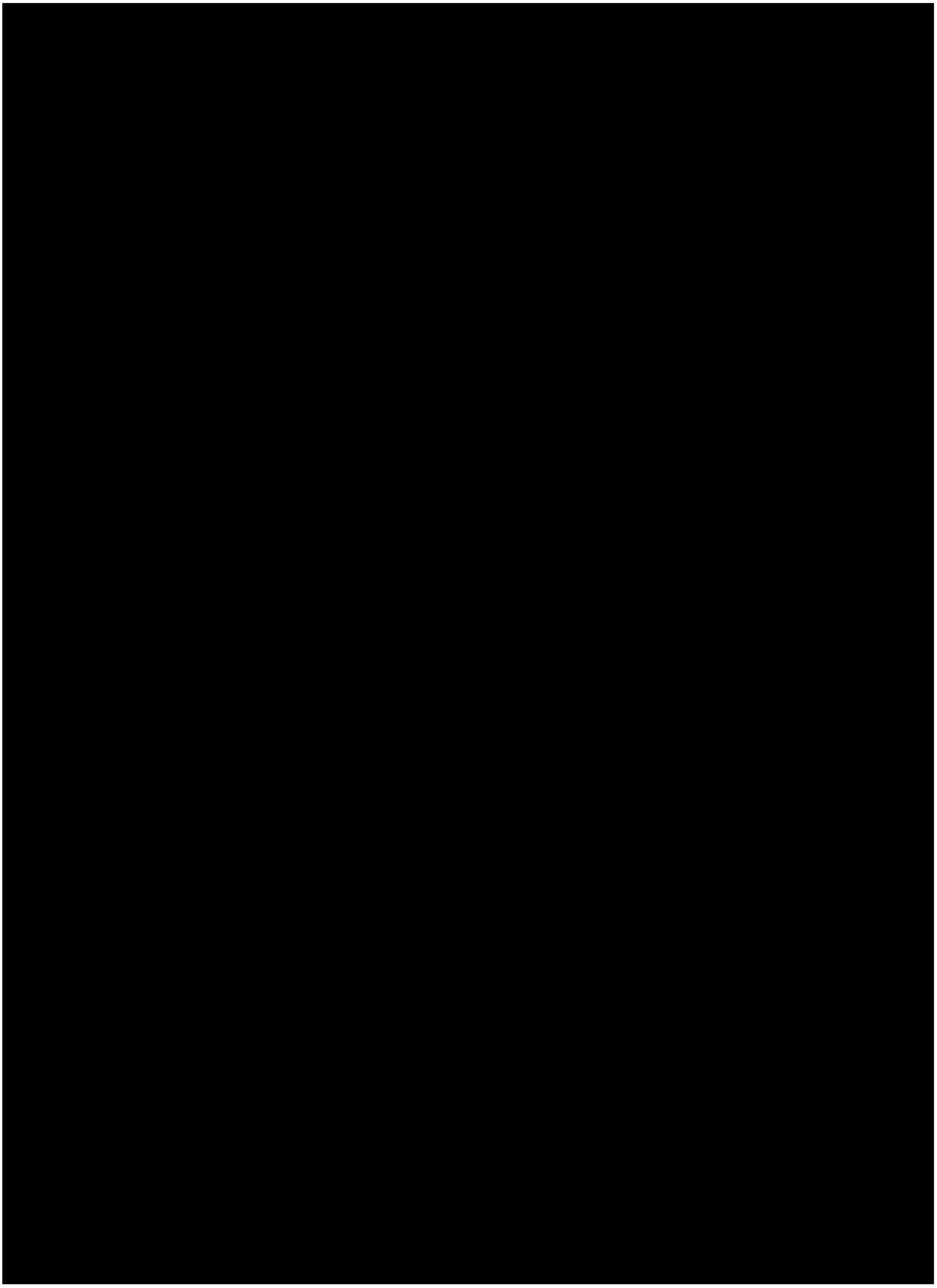
Additionally, summary statistics will be provided for all the visits till Week 52 for all patient-reported outcomes. Graphical representation will also be performed if required.

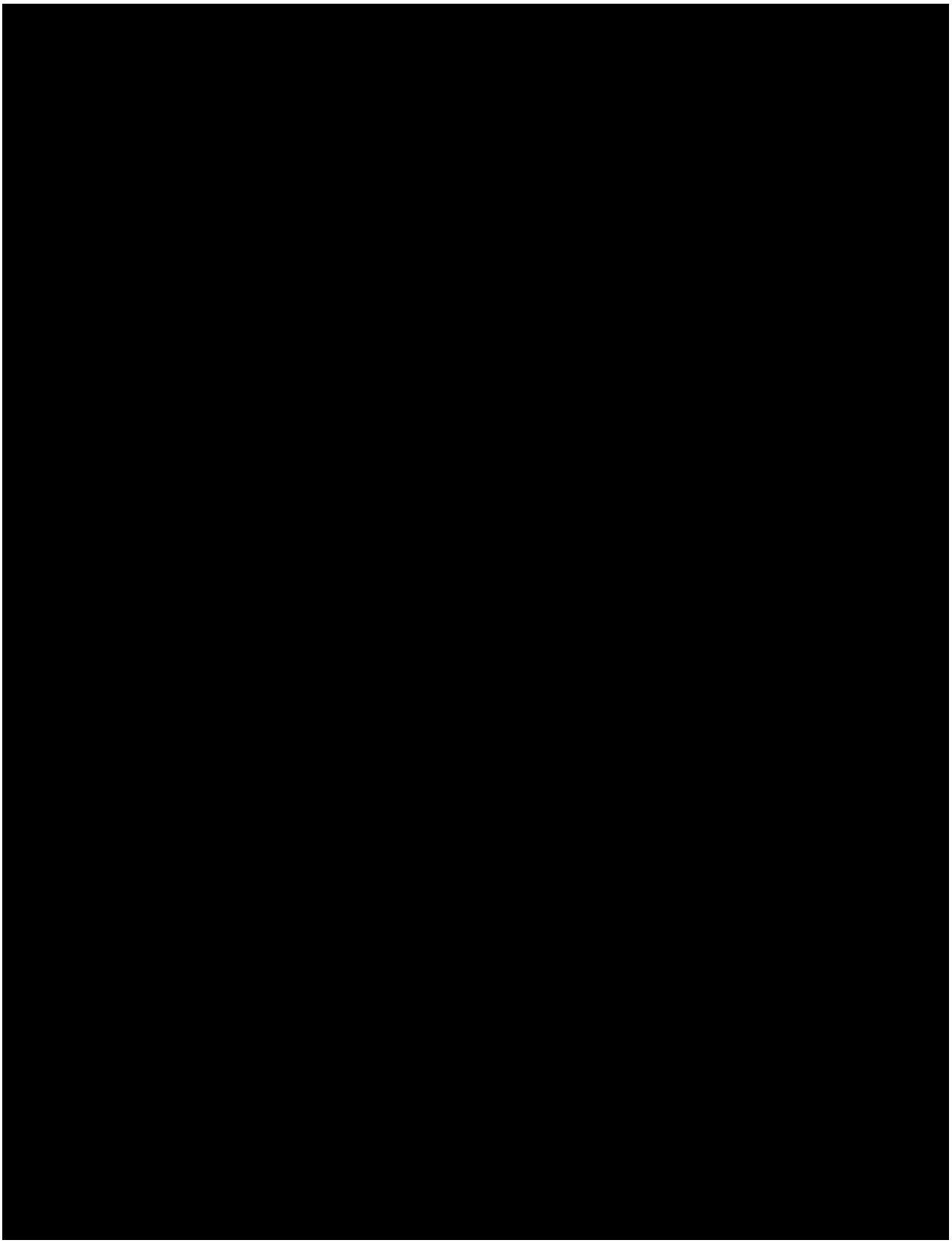
2.12 Biomarkers

Not Applicable.









3 Sample size calculation

The selected criterion for the primary objective, the ASAS 20 score, is intended to be used in patients with axial skeleton involvement. Consequently, secukinumab data available from previous studies on this outcome measure, related to AS patients, can be taken into account. Compared to PsA patients, in AS patients the peripheral joints involvement is less pronounced. Thus, the ASAS 20 score for AS patients is expected to capture information entirely related to the axial skeleton involvement. Patients with PsA, who will be included in the present study, are characterized by concomitantly experiencing axial and peripheral joints disease. Thus, the ASAS 20 score is expected to also reflect the peripheral joints components.

To assume the magnitude of ASAS 20 response for PsA patients treated with secukinumab data from CAIN457F2310 (AS patients) and the CAIN457F2312 (PsA patients) have been considered.

The CAIN457F2310 study compared secukinumab to placebo in AS patients, and the ASAS 20 response rate at Week 12 was 57% for 150 mg secukinumab and 28% for placebo (300mg secukinumab was not tested). These results are a basis to extrapolate the expected results for the current study.

In a phase 3 study of Secukinumab in PsA patients, CAIN457F2312, the performance of 300 mg secukinumab is, compared to 150 mg secukinumab, numerically better in the achievement of the ACR 20 score. Assuming comparable trends in treatment response of the spine and the peripheral joints, a slightly different response between the 300 mg and the 150 mg treatment group was chosen. In addition, from data available in the literature (Lubrano and Spadaro 2012) it appears that the spinal involvement in PsA is milder compared to AS in terms of inflammation and impact on physical function, so that it can be expected that PsA patients might more easily achieve an ASAS20 score compared to AS patients. Similarly, we can assume that placebo response rates in AxPsA patients may be higher compared to AS.

For the 150 mg secukinumab treatment group a response rate of 57% is expected at Week 12.

For the 300 mg secukinumab treatment group a response rate of 60% is expected at Week 12.

An overall type I error (2-sided) 5% will be used to control type I error. Since two secukinumab doses will be tested versus placebo in a hierarchical manner, no type-I-error adjustment is required for each comparison with respect to the primary endpoint (ASAS 20 response at Week 12). To achieve 92% power and assuming conservatively a response rate of 40% in the placebo group, at least 150 patients per group would be needed under equal allocation to show a response rate of 60% in the secukinumab 300 mg group. Using the same number of patients per group, the second test will have at least 80% power to detect a difference, if the true response rates are 57% in secukinumab 150 mg group and 40% in placebo. The above sample size calculation is based on Fisher's exact test.

To compensate for drop-outs and protocol violations, 165 patients per group (=495 total) should be recruited into this trial.

SAS® version 9.4 software was used for the calculation of sample size.

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 start date imputation

	MON	**MON < CFM**	**MON = CFM**	**MON > CFM**
	MISSING			
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

AE end date imputation

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 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 (study treatment follow-up period date, 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.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

5.1.3 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < study treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY).
- Else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY).
- If DIAG year = study treatment start date year and (DIAG month is missing OR DIAG month is equal to study treatment start month), the imputed DIAG date is set to one day before study treatment start date.

5.1.4 Concomitant medication date imputation

Concomitant medication (CMD) start date imputation (#IMPUTMED)

Rules for imputing the CMD start date:

This algorithm is used when *event* is the partial start date of the concomitant medication, non- drug therapy/procedure, or prior study indication therapy.

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSDT)	Not used	TRTM	TRTY

The following matrix explains the logic behind the	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY	**(C2)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain	**(C1)** Uncertain

MISSING				
YYYY<TRTY	**(D)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start	**(A)** Before Treatment Start
YYYY=TRTY	**(C2)** Uncertain	**(A)** Before Treatment Start	**(C1)** Uncertain	**(B)** After Treatment Start
YYYY>TRTY	**(E)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start	**(B)** After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date **prior** to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date **after** Treatment Start Date
Uncertain	Partial date **insufficient to determine** relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY
(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ‘ ’ THEN TRTSDT+1
(D)	01JULYYYY
(E)	01JANYYYY

Concomitant medication end date imputation

If not ongoing then –

- If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
- Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the following options: treatment follow up period date, 31DECYYYY, date of death.
- If the CM end date day is missing, the imputed end date should be set to the earliest of the following: treatment follow up period date, last day of the month, date of death.
- If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

Concomitant medication date flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else

M – If month of the imputed date is not equal to MON

else D

5.1.4.1 Prior therapies date imputation

Not applicable

5.1.4.2 Post therapies date imputation

Not applicable

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 of SAP.

5.4 Statistical methodology and assumptions

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

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

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

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

Then the lower limit is

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

and the upper limit is

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

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

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

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

For an investigational drug group with n1 subjects at risk, independent from the control group (e.g. placebo or comparator) with n0 subjects at risk, of whom x1 and x0 experience a certain event with probability π1 and π0 respectively, the odds ratio is estimated as

$\frac{p_1/(1-p_1)}{p_0/(1-p_0)}$ with p1= x1/n1 and p0=x0/n0. A conditional exact 100*(1-α)% confidence interval can be obtained by using the SAS procedure PROC FREQ with statement EXACT

OR. However, to be able to adjust for covariates odds ratios will primarily be obtained from PROC GENMOD.

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 tj (j=1,...,n) to the first occurrence of a certain event is observed, or if the event was not experienced, the (censored) time to the end of the observation period. The sequence of first occurrences of an event will be modeled to follow approximately a Poisson process with constant intensity θ. The rate parameter θ will be estimated as λ=D/T, where

$$T = \sum_{j=1}^{n} t_j$$

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

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

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

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

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 16-3 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) 110 (10 days into 2nd trt)	Placebo: 50 days (event) 150 mg: 10 days (event) Any AIN: 10 days (event)

5.5 Score derivations and response criteria

5.5.1 Assessment of Spondyloarthritis International Society (ASAS)

The ASAS response measures consist of the following assessment domains (Sieper et al 2009):

1. Patient's global assessment of disease activity measured on a VAS scale.

2. Patient's assessment of IBP, represented by either total or nocturnal pain scores, both measured on a VAS scale.

3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale.

4. Morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scale.

ASAS response criteria (ASAS 20)

The ASAS Response Criteria (ASAS 20) was defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 10 in at least 3 of the 4 main domains and no worsening of ≥ 20% and ≥ 1 unit on a scale of 10 in the remaining domain.

ASAS response criteria (ASAS 40)

The ASAS 40 response was defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least 3 of the 4 main domains and no worsening at all in the remaining domain.

5.5.3 Bath ankylosing spondylitis disease activity index (BASDAI)

The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of axSpA:

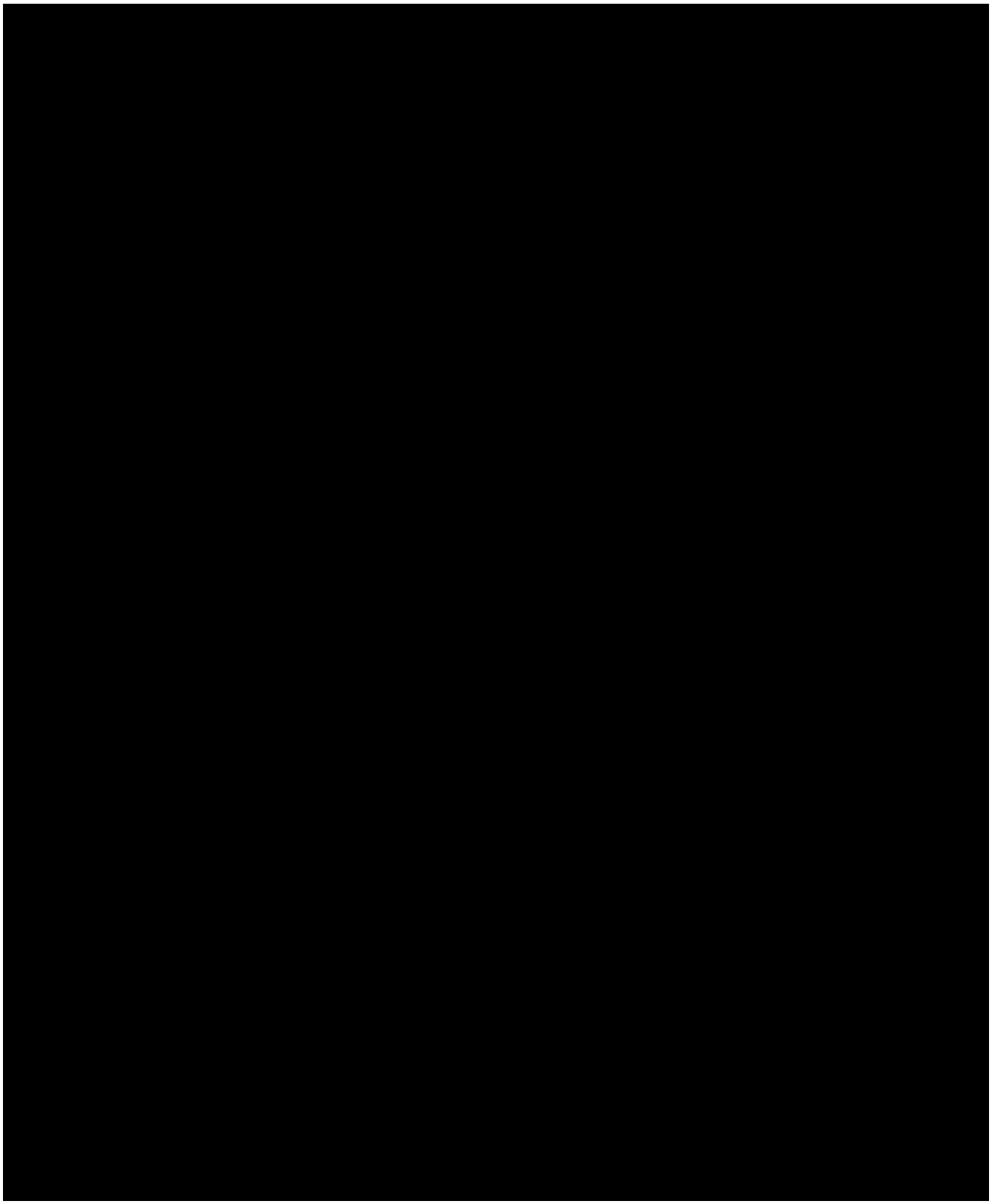
1. Fatigue
2. Spinal pain
3. Joint pain/swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

To give each symptom equal weighting, the mean (average) of the 2 scores relating to morning stiffness is taken (questions 5 and 6). The resulting 0 to 10 score is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0-10 BASDAI score. If one or more items are unanswered, the average of the non-missing items is used for the total score.

BASDAI 50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the Baseline total BASDAI score

5.5.4 Bath ankylosing spondylitis functional index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the 0 scales gives the BASFI score a value of between 0 and 10.



[redacted]

5.5.6 Health assessment questionnaire-disability index (HAQ-DI)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ (Health Assessment Questionnaire – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty [1], much difficulty [2], and unable to do [3].

Scoring for the eight functional categories and overall disability index scoring will be performed as follows:

There are eight categories; first score within each category:

- Dressing and Grooming, includes items 1 and 2
- Arising, includes items 3 and 4
- Eating, includes items 5, 6 and 7
- Walking, includes items 8 and 9
- Hygiene, includes items 10, 11, and 12
- Reach, includes items 13 and 14
- Grip, includes items 15, 16 and 17
- Activities, includes items 18, 19, and 20

The score for each category will be the single response within the category with the highest score (greatest difficulty). For example, in the "Eating" category, there are two answers (one for each item). If "Cut your food with a knife or fork" is marked as "3" and "Lift a full cup or glass to your mouth" is marked as "0", then the score for the "Eating" category would be "3" (the response indicating the greatest difficulty within the category). If a component question is left blank or the response is too ambiguous to assign a score, then the score that that category will be determined by the remaining completed question(s). However, if **any** "aids or devices" and/or "help from another person" items at the bottom of each page are checked, the category to which they apply will be adjusted upward to "2". If the basic score is **already** "2" or "3", the score remains unchanged. "Aids or devices" and "help from another person" can **only** change a category's score to "2"; they do **not** change the score to a "1" or a "3".

The score for the disability index will be the mean of the eight category scores. If more than two of the categories, or 25%, are missing, scale will not be scored. Otherwise, divide the sum

of the categories by the number of answered categories. The higher score indicates greater disability.

HAQ-DI response is defined by an improvement of at least 0.35 score points compared to baseline.

5.5.7 American college of Rheumatology (ACR) response

A patient will be considered as improved according the ACR 20 criteria if she/he has at least 20% improvement in the 2 following measures:

- Tender joint count (TJC)
- Swollen joint count (SJC)

and at least 3 of the following 5 measures：

- Patient's assessment of pain
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Health assessment questionnaire (HAQ©) score
- C-reactive protein (CRP) or erythrocyte sedimentation rate (note: CRP only will be assessed in this study)

If the number of joints for which data were available (e.g., T) is less than 78/76 for the tender/swollen joint assessment, the number of tender/swollen joints (e.g., t) will be scaled up proportionately (i.e., 78*t/T or 76*t/T for tender or swollen joint count).

5.5.8 ASAS Health Index

The ASAS health index is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree").

Each statement on the ASAS Health Index is given a score of 1 = I agree OR 0 = I do not agree. All item scores are summed up to give a total score that ranges from 0 (good functioning) to 17 (poor functioning). Items No 7 and 8 are not applicable for all patients. For those patients who ticked the response "not applicable", the sum score is analysed based on n=16 or n=15, respectively.

A total score can be analysed if no more than 20% of the data are missing. The total score is

calculated as follows for respondents with one to a maximum of three missing responses：

$$sumscore = \frac{x}{17 - m} \times 17$$

x = Item summation score

m = Number of missing items

Cases with more than three missing responses cannot be allocated a total score.

5.5.9 Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index

SPARCC assessments will be performed for following entheses sites, where tenderness at each site is quantified on a dichotomous basis: 0=non-tender and 1=tender. The score is obtained by summing up these values and the range of score is 0-16.

Greater trochanter	R/L
Quadriceps tendon insertion into the patella	R/L
Patellar ligament insertion into the patella and tibial tuberosity	R/L
Achilles tendon insertion	R/L
Plantar fascia insertion	R/L
Medial epicondyles	R/L
Lateral epicondyles	R/L
Supraspinatus insertion	R/L

If the number of entheses sites for which data were available (e.g., T) is less than 16 for the SPARCC assessment, the number of tender entheses sites (e.g., t) will be scaled up proportionately (i.e., 16*t/T for SPARCC score).

5.5.10 FACIT-Fatigue©

The FACIT-Fatigue© is a 13-item questionnaire. The following instructions are to be followed to calculate fatigue subscale score:

- Perform reversals as indicated for the recorded responses and sum individual items to obtain a score.
- Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
- The higher the score, the better the QOL.

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (i.e., 7 or more items were answered).

Subscale	Item Code	Reverse item?		Item response	Item Score
FATIGUE SUBSCALE	HI7	4	-	_____	=_____
	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

5.6 Statistical models

5.6.1 Primary analysis

The primary statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the Secukinumab 300 mg treatment group versus placebo group.

The primary analyses will be conducted via logistic regression with treatment and concomitant MTX intake status as factors. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab 300 mg treatment group to placebo group at Week 12.

SAS Code for logistic model

```
Proc logistic data=aaa;
Class TRT STRATA / param=glm;
Model AVAL = TRT 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 12, 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.

```
Proc logistic data=aaa exactonly;
```

```
Class TRT STRATA / param=glm;
Model AVAL = TRT STRATA;
Exact TRT / estimate=both;
Ods output exactoddsratio=exactoddsratio;
Run;
```

Missing data for ASAS 20 response for data up to Week 12 will be handled by multiple imputations technique.

Multiple Imputation

A multiple imputation will be performed based on MAR by treatment group for baseline weight, baseline and post-baseline of each parameter for visits up to the primary time point of 12 weeks using Markov Chain Monte Carlo (MCMC) method with EM algorithm.

Impute the missing values 100 times (NIMPUTE) with a seed=457<studycode> as shown below:

```
proc mi data= min=<min of scale> max=<max of scale> out=imp minmaxiter=100000
nimpute=100 seed=4572310;
by trt;
var weight_base var1_base var1_week1-var1_week16;
mcmc chain=multiple initial=em;
run;
```

If needed repeat for each component necessary to calculate the final score, e.g. as follows:

```
proc mi data=imp min=<min of scale> max=<max of scale> out=imp2 minmaxiter=100000
nimpute=1 seed=4572310;
by trt _imputation_;
var weight_base var2_base var2_week1-var2_week16;
mcmc chain=multiple initial=em;
run;
```

The score and ASAS response can now be calculated based on the complete data. The response rate will be calculated for each imputation and then combined using Rubin's rules. In order to calculate the response rate for each imputation, PROC FREQ will be used as follows.

Calculate binomial proportion and standard error for each imputation.

```
proc freq data=<ASAS20>;
by treat visit _imputation_ ;
tables <response> / binomial (level=2 cl=wilson correct) ;
ods output BinomialProp=imp_bpr;
run;
```

Transpose the dataset for subsequent use with PROC MIANALYZE.

```
proc transpose data=imp_bpr out=imp_trs(drop=_name_) ;
by treat visit _imputation_ ;
var nvalue1; id name1; idlabel label1;
run;
```

Apply LOGIT transformation: y=log(p/(1-p)) and std. err. transformation: <new se> = se/(p*(1-p))

```
data logit;
set imp_trs(rename=(_bin_=p e_bin=se));
by treat visit _imputation_ ;
lmean=log(p/(1-p));
lse=se/(p*(1-p));
run;
```

The transformed binomial proportion estimates and standard errors are combined by applying Rubin's rules for multiple imputed data sets.

```
proc mianalyze data=logit;
by treat visit ;
modeleffects lmean;
stderr lse;
ods output ParameterEstimates=logitres;
run;
```

The combined data should be transformed back using the following formula: p=1/(1+exp(-y))

```
data miexpres;
set logitres;
by treat visit ;
resti = 1/(1+exp(-estimate));
rlow = 1/(1+exp(-lclmean));
rupp = 1/(1+exp(-uclmean));
run;
```

Of note, sometimes all responses may be imputed to 0 or 1 at a given combination of response variable, treatment group and visit. Such cases should be considered separately. The combined final response rate would be the same as the original response but the 95% CI will be undefined.

The odds ratio will be derived using GENMOD for each imputation, then combined using Rubin's rules again.

```
proc genmod data = asas20_mi descending;
by avisitn _imputation_;
class trt_ TNFRESN ;
model aval = trt_ TNFRESN weight / link=logit dist=bin;
lsmeans trt_ / diff;
estimate 'AIN457 75mg mg vs Placebo' trt_ 1 0 -1;
estimate 'AIN457 150mg mg vs Placebo' trt_ 0 1 -1;
ods output Estimates=imp_est;
run;

proc mianalyze data=imp_est;
by avisitn trt_ ;
modeleffects LBetaEstimate;
stderr StdErr;
ods output ParameterEstimates=res;
run;
```

For sensitivity analysis, the above code will be used for non-responder imputation.
In addition to that, the above analysis will also be performed for each baseline variables (e.g: sex, age class, disease severity at Baseline).

Non-parametric ANCOVA model

A non-parametric ANCOVA model (Koch 1998) will be used as sensitivity analysis for ASAS 20 and possibly also for continuous endpoints that are not normally distributed. The macro NParCov3 will be used (Zink 2012).

For continuous response variable, the macro call will be as follows:

```
%NParCov3(OUTCOMES = response, COVARS = weight baseline, C = 1, HYPOTH =
ALT,
STRATA = TNFα status, TRTGRPS = treatment, TRANSFORM = NONE, COMBINE =
FIRST, DSNIN = RESP, DSNOUT = OUTDAT);
```

Data set _OUTDAT_DEPTEST provides results for the treatment difference, and _OUTDAT_CI provides a 95% confidence interval for the treatment estimate.

For binary response variable, the macro call will be as follows:

```
%NParCov3(OUTCOMES = response, COVARS = weight, C = 1, HYPOTH = ALT,
STRATA = TNFα status, TRTGRPS = treatment, TRANSFORM = LOGISTIC, COMBINE =
FIRST, DSNIN = RESP, DSNOUT = OUTDAT);
```

The odds ratio and confidence interval are to be obtained from _OUTDAT_RATIOCI.

5.6.2 Key secondary analysis

The statistical hypothesis for ASAS 20 being tested is that there is no difference in the proportion of patients fulfilling the ASAS 20 criteria at Week 12 in the Secukinumab 150 mg treatment group versus placebo group, after superiority is demonstrated for secukinumab 300 mg to placebo at Week 12.

The above code will be used for key secondary analysis.

5.6.1 Secondary analyses

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, 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 STRATA;
model response = TRT STRATA BASE / s;
lsmeans TRT / diff;

run;
```

In addition, key secondary variables measured at all post baseline visits up to Week 52 will be analyzed using longitudinal mixed effects ANCOVA model with treatment, baseline stratification factor and analysis visit as factors; and weight, baseline value, treatment by visit and baseline by visit interactions as covariates. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

SAS code for mixed model:

```
proc mixed data=aaa;
class TRT USUBJID AVISITN STRATA;
model CHG=TRT STRATA AVISITN WEIGHT BASE TRT*AVISITN BASE*AVISITN
/ s ddfm=kr;
lsmeans TRT*AVISITN / diff cl;
repeated AVISITN / type=un subject=USUBJID;
Run;
```

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.

2. change type=un to type=cs. If still no convergence, perform step 3.

3. remove covariates in the following order until convergence: WEIGHT, BASE*AVISITN, STRATA.

Crude and adjusted incidence rates

The SAS codes of crude and adjusted incidence rates and confidence intervals will be referred from the MAP or AIN457F2310 M3.

5.7 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01	Informed consent not obtained before study inclusion	EXCLUDE FROM FAS AND SAF	3
INCL02	Informed consent not signed or missing or date of signing ICF is missing.	EXCLUDE FROM FAS AND SAF	3
INCL03	BASDAI score is < 4 at baseline	EXCLUDE FROM FAS	1
INCL04	Spinal Pain VAS score is < 40 at Baseline	EXCLUDE FROM FAS	1
INCL05	No inadequate response to at least 2 NSAIDs over a period of 4 weeks	EXCLUDE FROM PPS	4
INCL06	Subject <18 years of age	EXCLUDE FROM FAS AND SAF	3
INCL07	Patient has no axial PsA diagnosis at screening	EXCLUDE FROM PPS	4
INCL08	CASPAR score is < 3 at screening	EXCLUDE FROM PPS	4
INCL09	Patient is a lactating woman	INCLUDE IN EVERYTHING	0
EXCL01	Evidence of ongoing infectious or malignant processes, obtained within 3 months prior to Screening by Chest X ray or MRI	INCLUDE IN EVERYTHING	0
EXCL02	Patient takes high potency opioid analgesics	EXCLUDE FROM PPS	4
EXCL03	History of exposure to other IL-17 or IL-23 inhibitor biologic drug(s)	EXCLUDE FROM PPS	4
EXCL04	History of exposure to previous biologic DMARD(s)	EXCLUDE FROM PPS	4

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL05	Current treatment with DMARD(s) other than MTX at baseline	EXCLUDE FROM PPS	4
EXCL06	Any therapy by intra-articular injections within 4 weeks before randomization	EXCLUDE FROM PPS	4
EXCL07	Patient taking NSAIDs is not on a stable dose for at least 2 weeks before randomization.	EXCLUDE FROM PPS	4
EXCL08	Patient taking systemic corticosteroids is not on a stable dose ≤ 10 mg/day of prednisone for at least 2 weeks before randomization.	EXCLUDE FROM PPS	4
EXCL09	Patients who are on MTX (≤ 25 mg/week) who are not on a stable dose for at least 4 weeks before randomization	EXCLUDE FROM PPS	4
EXCL10	Patients on MTX who are not on folic acid supplementation at randomization	INCLUDE IN EVERYTHING	0
EXCL11	Patients who are on DMARD(s) other than MTX and who have not discontinued the DMARD(s) 4 weeks before randomization (8 weeks for leflunomide unless cholestyramine washout has been performed)	EXCLUDE FROM PPS	4
EXCL12	Active ongoing inflammatory diseases other than psoriais that might confound the evaluation of the benefit of secukinumab therapy	EXCLUDE FROM PPS	4
EXCL13	Positive pregnancy test result before randomization	INCLUDE IN EVERYTHING	0
EXCL14	History of an ongoing, chronic or recurrent infectious disease	EXCLUDE FROM PPS	4
EXCL15	Subject enrolled with latent TB and without therapy initiated as per local guidelines.	INCLUDE IN EVERYTHING	0
EXCL16	Subject enrolled with active TB.	EXCLUDE FROM PPS	4
EXCL17	Use of any other investigational drug within 4 weeks prior to Visit 2 or within a period of 5 half-lives of the investigational drug	EXCLUDE FROM PPS	4
EXCL18	Any intramuscular or intravenous (i.v.) corticosteroid treatment within 4 weeks before randomization	EXCLUDE FROM PPS	4

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL19	Previous treatment with any cell-depleting therapies.	EXCLUDE FROM PPS	4
EXCL20	Significant medical problems excluded by the protocol such as but not limited to excluded cardiovascular diseases.	EXCLUDE FROM PPS	4
EXCL21	History of renal trauma, glomerulonephritis, or patients with 1 kidney only	INCLUDE IN EVERYTHING	0
EXCL22	Serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L) prior to randomization	INCLUDE IN EVERYTHING	0
EXCL23	Subject enrolled with WBC, platelets, neutrophils or hemoglobin less than values detailed in protocol at screening.	INCLUDE IN EVERYTHING	0
EXCL24	Active systemic infections during the 2 weeks prior to randomization (exception: common cold) or any infection that reoccurs on a regular basis	INCLUDE IN EVERYTHING	0
EXCL25	Past medical history record of or current infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C prior to baseline	INCLUDE IN EVERYTHING	0
EXCL26	History of lymphoproliferative disease / known malignancy / history of malignancy of any organ system within the past 5 years.	INCLUDE IN EVERYTHING	0
EXCL27	History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to baseline	INCLUDE IN EVERYTHING	0
EXCL28	Administration of live vaccines within 6 weeks preceding randomization	INCLUDE IN EVERYTHING	0
[redacted]			
EXCL31	Women of childbearing potential who do not agree to be compliant with protocol specified contraception	INCLUDE IN EVERYTHING	0
EXCL32	History of hypersensitivity reactions to any of the excipients	INCLUDE IN EVERYTHING	0
EXCL33	Underlying condition at enrolment which immunocompromised the patient and/or places the patient at unacceptable risk.	INCLUDE IN EVERYTHING	0
EXCL34	Any single parameter (ALT, AST, AP) must not exceed 2 × upper limit of normal (ULN) prior to randomization.	INCLUDE IN EVERYTHING	0
EXCL35	In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L) prior to randomization.	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL36	Current severe progressive or uncontrolled disease, which renders the patient unsuitable for the trial.	INCLUDE IN EVERYTHING	0
EXCL37	Medical or psychiatric condition, which would preclude the patient from adhering to/ completing the protocol.	INCLUDE IN EVERYTHING	0
EXCL39	Evidence of tuberculosis infection as defined by a positive or indeterminate QuantiFERON tuberculosis (TB) Gold test (QFT) at Screening, but no workup performed	INCLUDE IN EVERYTHING	0
WITH01	Positive pregnancy test result but patient has not discontinued the study.	INCLUDE IN EVERYTHING	0
WITH02	Uncontrolled hypertension (≥ 160/95 mmHg) but patient has not discontinued the study.	INCLUDE IN EVERYTHING	0
WITH03	Administration of live vaccines during the study period and patient not discontinued.	INCLUDE IN EVERYTHING	0
TRT01	Less than 2 injections of secukinumab or matching placebo administered and the reason is not “Adverse event”.	EXCLUDE FROM PPS	4
TRT02	More than two injections of secukinumab or matching placebo administered on the same day.	EXCLUDE FROM PPS	4
TRT03	Incorrect study medication administered.	EXCLUDE FROM PPS	4
TRT07	Use of medication which could have been damaged based on storage conditions / temperature deviations	EXCLUDE FROM PPS	4
TRT08	Minimum interval between two administrations of study drug was not respected	INCLUDE IN EVERYTHING	0
COMD01	Treatment with biological immunomodulating agents at any time during the study	EXCLUDE FROM PPS	4
COMD02	Current treatment with DMARD(s) other than MTX at any time during the study	EXCLUDE FROM PPS	4
COMD03	Any therapy by intra-articular injections during the study.	EXCLUDE FROM PPS	4
COMD04	Patient taking NSAIDs is not on a stable dose during the study.	EXCLUDE FROM PPS	4
COMD05	NSAIDs intake during 24h before a visit involving a disease activity assessment	EXCLUDE FROM PPS	4
COMD06	Patient taking systemic corticosteroids is not on a stable dose ≤ 10 mg/day of prednisone during the study.	EXCLUDE FROM PPS	4
COMD07	Patients taking MTX at an unstable dose during the study.	EXCLUDE FROM PPS	4
COMD07a	Patients taking MTX 48 hours before a clinical laboratory evaluation	EXCLUDE FROM PPS	4

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
COMD08	Patients on leflunomide any time during the study.	EXCLUDE FROM PPS	4
COMD09	Use of any investigational drug and/or devices during the study	EXCLUDE FROM PPS	4
COMD10	Any intramuscular or intravenous (i.v.) corticosteroid treatment during the study.	EXCLUDE FROM PPS	4
COMD12	Patients receiving analgesics other than NSAIDs, paracetamol/acetaminophen and low strength opioids PRN during the study.	EXCLUDE FROM PPS	4
COMD13	Patient is taking systemic corticosteroids > 10 mg/day of prednisone or equivalent.	EXCLUDE FROM PPS	4
COMD14	Patient taking MTX > 25 mg/week during the course of the study.	EXCLUDE FROM PPS	4
[redacted]			
OTH02	Patient did not complete ASAS component at baseline visit.	INCLUDE IN EVERYTHING	0
OTH02a	Patient did not complete ASAS component at week 12 visit.	EXCLUDE FROM PPS	4
OTH06	PRO data was not collected according to the protocol. A non-validated process was used to collect PRO data	EXCLUDE FROM PPS	0
OTH07	Data not intended for the study have been submitted to a vendor database	INCLUDE IN EVERYTHING	0
OTH08	Maximum protocol timelines were not adhered too	INCLUDE IN EVERYTHING	0

The following criteria will lead to exclusion of subjects from the respective analysis sets, as they might have some impact on the outcome of the study.

Deviation text description	Severity code	Excluded from analysis set
Compliance to study medication < 80% or >120%	4	Exclude from PPS

Table 5-2 Analysis set exclusions based on population codes

Analysis set	Population codes that cause a subject to be excluded
RAN	NA
SAF	2, 3
FAS	1, 3
PPS	1, 4
[redacted]	[redacted]

Table 5-3 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
4	EXCLUDE FROM PER-PROTOCOL SET (PPS)
[redacted]	[redacted]

6 Reference

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