NOVARTIS

Clinical Development

AIN457/Secukinumab

CAIN457H3301 / NCT03136861

SKIPPAIN (Speed of onset of SecuKinumab-Induced relief from Pain in Patients with AxIal SpoNdyloarthritis) A 24-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in controlling spinal pain in patients with axial spon.dyloarthritis

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
18-May-2018		CTT decided to modify various sections and related analysis	Some analysis added to exploratory endpoint. Analyses related to primary and secondary endpoint are modified. Overall safety set is included.	Overall SAP document is modified and hence impacted.
16-Apr-2019		To impute partial dates for calculation of duration since the subject has been identified for disease history	Added Medical History date of diagnosis imputation	Added new section 5.1.4
16-Apr-2019		Clarified that subjects who are re-assigned the treatment in 2nd period are included in FAS-TP2	Revised FAS-TP2 analysis set definition	2.2
29-May-2019		Impute partial CM and AE end date	Added imputation rule for CM end date and AE end date	Added text for the same in section 5.1.2 & 5.1.3

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List of abbreviations

AE	Adverse event
AESI	Adverse Event of Special Interest
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase
ANOVA	Analysis of Variance
anti-TNFα	anti-Tumor Necrosis Factor alpha
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
ATC	Anatomical Therapeutic Classification
axSpA	axial SpondyloArthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body mass index
bpm	Beats per minute
CD	Cluster of Differentiation
CI	Confidence interval
CMD	Concomitant medication
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study report
DAR	Drug administration record
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS-TP1	Full Analysis Set for Treatment Period 1
FAS-TP2	Full Analysis Set for Treatment Period 2
hCG	Human Chorionic Gonadotropin
HLA-B27	Human Leukocyte Antigen-B27
HLT	High Level Term
HR-QoL	Health-related quality of life
ICF	Informed Consent Form
IEC	Independent Ethics Committee
i.v.	Intravenous
LFT	Liver Function Test (raised serum transaminase and/or bilirubin levels)
MCII	Minimal Clinically Important Improvement
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed Model Repeated Measures
MRI	Magnetic resonance imaging
NMQ	Novartis MedDRA Query

NSAID(s)	Nonsteroidal Anti-Inflammatory Drug(s)
NRS	Numerical Rating Scale
PASS	Patient Accepted Symptoms State
PD	Protocol deviation
PFS(s)	PreFilled Syringe(s)
PRO	Patient Reported Outcome
PT	Preferred Term
RAN	Randomized set
SAE	Serious Adverse Event
SAF-TP1	Safety Set for Treatment Period 1
SAF-TP2	Safety Set for Treatment Period 2
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SpA	SpondyloArthritis
TB	Tuberculosis
TBL	Total Bilirubin
TNF	Tumor Necrosis Factor
TNFα-IR	Tumor Necrosis Factor α Inadequate Responder
ULN	Upper Limit of Normal

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 CAIN457H3301.

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 (clinical study report). 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 CAIN457H3301

1.1 Study design

This is a 24-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in controlling spinal pain in patients with axSpA. The study will consist of 2 treatment periods: a double-blind, placebo-controlled period from Baseline to Week 8 (i.e. Treatment Period 1) and a double-blind secukinumab treatment period from Week 8 to Week 24 (i.e. Treatment Period 2). At Baseline, patients will be randomized to either secukinumab 150 mg or placebo. At Week 8, patients will be re-randomized and re-assigned respectively to 1 of 5 treatment arms to receive either secukinumab 150 mg or secukinumab 300 mg.

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

Planned number of patients and randomization

It is intended that a total of 352 patients (264 in secukinumab 150 mg group and 88 in the placebo group) will be recruited to compensate dropouts and protocol violators.

Patient eligibility criteria will be assessed during the Screening Period, which will occur for up to 10 weeks prior to randomization.

Treatment Period 1

At Baseline, patients whose eligibility is confirmed will be randomized to receive double-blind treatment with either secukinumab 150 mg or placebo (3:1) in Treatment Period 1 (Baseline to time of study drug administration at Week 8):

- **Group A**: secukinumab 150 mg (1 x 1.0 mL) s.c. administered at Baseline, Week 1, 2, 3 and 4
- **Group B**: placebo (1 x 1.0 mL) s.c. administered at Baseline, Week 1, 2, 3 and 4

Secukinumab 150 mg and matching placebo will be provided as 1.0 mL pre-filled syringes (PFSs).

On each treatment day during Treatment Period 1, one s.c. injection with either secukinumab 150 mg or placebo will be administered via PFSs.

Treatment Period 2

At Week 8, patients will enter Treatment Period 2 (Week 8 to Week 24). Patients randomized to Group A (secukinumab 150 mg) at Baseline will be assessed for the achievement of spinal pain NRS score and will be classified as responders (spinal pain NRS score < 4) or non-responders (spinal pain NRS score ≥ 4). Responders will be re-assigned to 1 treatment arm (Arm A1) to continue double-blind treatment with secukinumab 150 mg every 4 weeks from Week 8 to Week 24 (last dose administered at Week 20). Non-responders will be separately re-randomized to 1 of 2 arms to receive double-blind treatment with either secukinumab 150 mg or secukinumab 300 mg every 4 weeks starting at Week 8 up to Week 24 (last dose administered at Week 20).

Patients on secukinumab 150 mg who achieve spinal pain NRS score < 4 at Week 8 will be re-assigned to continue secukinumab 150 mg every 4 weeks (Arm A1)

- **Arm A1**： secukinumab 150 mg (1 x 1.0 mL) plus placebo (1 x 1.0 mL) administered at Week 8, 12, 16 and 20

Patients on secukinumab 150 mg who do not achieve spinal pain NRS score < 4 at Week 8 will be re-randomized to continue secukinumab 150 mg every 4 weeks (Arm A2) or to escalate to secukinumab 300 mg every 4 weeks (Arm A3):

- **Arm A2**: secukinumab 150 mg (1 x 1.0 mL) plus placebo (1 x 1.0 mL) administered at Week 8, 12, 16 and 20
- **Arm A3**: secukinumab 300 mg (2 x 1.0 mL) administered at Week 8, 12, 16, and 20

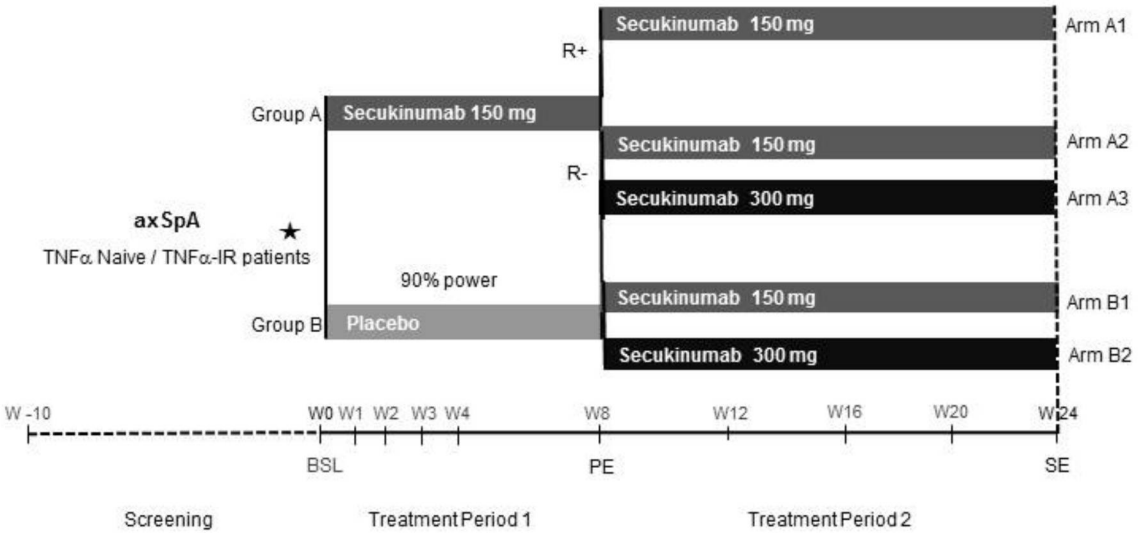
At Week 8, patients randomized to Group B (placebo) at Baseline will be re-randomized to either secukinumab 150 mg every 4 weeks (Arm B1) or secukinumab 300 mg every 4 weeks (Arm B2)

- **Arm B1**: secukinumab 150 mg (1 x 1.0 mL) plus placebo (1 x 1.0 mL) administered at Week 8, 12, 16 and 20
- **Arm B2**: secukinumab 300 mg (2 x 1.0 mL) administered at Week 8, 12, 16, and 20

During the study, patients will be required to self-administer secukinumab or placebo at all study visits and at home at Week 16.

On each treatment day during Treatment Period 2, two s.c. injections will be administered via PFSs either as 1 injection of secukinumab 150 mg and 1 injection of placebo, or 2 injections of secukinumab 150 mg. This is necessary to maintain the blind since secukinumab is supplied in 1.0 mL PFSs each containing 150 mg secukinumab, i.e. secukinumab 150 mg is supplied as 1 PFS and secukinumab 300 mg as 2 PFSs. Placebo to secukinumab will be supplied in 1.0 mL PFSs to match the active drug.

Figure 1-1 Study design



★Patients will be stratified at baseline based on whether they are naïve to TNFα inhibitors or had an inadequate response (including intolerance) to TNFα inhibitors.

R+ = responder, i.e. patient with spinal pain NRS score < 4

R- = non-responder, i.e. patient with spinal pain NRS score ≥ 4

axSpA=axial spondyloarthritis, BSL=baseline, PE=primary endpoint, SE=secondary endpoint, TNFα=tumor necrosis factor alpha, TNFα-IR=tumor necrosis factor α inadequate responder, W=week

Primary analysis time point

The primary analysis will be performed based on Week 8 assessment data. Average spinal pain NRS score will be considered as primary endpoint and will be analyzed for all applicable variables.

Interim analyses

No interim analysis is planned for this study.

The statistical analysis will be performed after all the patients have completed the study. Once all the data are complete and clean, the database will be locked and analyzed.

1.2 Study objectives and endpoints

Table 1.2-1 Objectives and related endpoints

Objective	Endpoint
Primary objective	
Superiority of secukinumab 150 mg compared to placebo in achieving a spinal pain score < 4 on a 0-10 NRS at Week 8.	Proportion of patients with a spinal pain NRS score < 4 at Week 8 in Group A compared to Group B.

Secondary objectives	
Superiority of secukinumab 150 mg compared to placebo in achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score < 4 at Week 8.	Proportion of patients with a BASDAI score < 4 at Week 8 in Group A compared to Group B.
Exploratory objectives	
Proportion of patients achieving a spinal pain score < 4 on a 0-10 NRS at Week 1, 2, 3 and 4 with secukinumab 150 mg compared to placebo.	Proportion of patients with a spinal pain NRS score < 4 in Group A compared to Group B at Week 1, 2, 3 and 4.
Proportion of patients in each treatment arm achieving a spinal pain score < 4 on a 0-10 NRS at Week 24.	Proportion of patients with a spinal pain NRS score < 4 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
Proportion of patients in each treatment arm achieving BASDAI score < 4 at Week 24.	Proportion of patients achieving a BASDAI score < 4 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
Proportion of patients in each of the treatment arms achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) score < 2.1 at Week 8 and Week 24.	Proportion of patients with a ASDAS score < 2.1 in Group A compared to group B at Week 8 and in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 8 and Week 24.
Proportion of patients in each treatment arm achieving ASDAS score < 1.3 at Week 8 and Week 24.	Proportion of patients with a ASDAS score < 1.3 in Group A compared to Group B at Week 8 and in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 8 and Week 24.
Mean change from Baseline in functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue©) score in patients on secukinumab 150 mg compared to placebo at Week 8.	FACIT-Fatigue© score in Group A compared to Group B at Week 8.
Mean change from Baseline in FACIT-Fatigue© score in each of treatment arm at Week 24.	FACIT-Fatigue© score in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
Proportion of patients in Arm A1 who have pain flares defined as NRS score > 6 at Week 12 or Week 24.	Proportion of patients who have pain flares, defined as NRS score > 6, in Arm A1 at Week 12 or Week 24.
Proportion of patients achieving a satisfactory Patient Acceptable Symptom State (PASS) at Week 1, 2, 3, 4 and 8 with secukinumab 150 mg compared to placebo.	Proportion of patients achieving a satisfactory PASS at Week 1, 2, 3, 4 and 8 in Group A compared to Group B.

Proportion of patients in each of treatment arm achieving a satisfactory PASS at Week 12, Week 20 and Week 24.	Proportion of patients achieving a satisfactory PASS at Week 12, Week 20 and Week 24 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2.
Spinal pain NRS score according to previous exposure to tumor necrosis factor (TNF) inhibitors at Week 1, 2, 3, 4, 8, 12 and 24	Proportion of patients achieving a spinal pain score < 4 for TNF-naïve patients compared to TNFα-IR patients at Week 1, 2,3, 4, 8, 12 and Week 24
Proportion of patients who responded to secukinumab 150 mg at Week 8 (i.e. spinal pain score < 4 on a 0-10 NRS) maintaining a response at Week 24.	Proportion of patients with spinal pain score < 4 on a 0-10 NRS at Week 8 maintaining a spinal pain score < 4 at Week 24.
Proportion of patients achieving an improvement in ASAS health index with secukinumab 150 mg compared to placebo at Week 8.	Proportion of patients achieving an improvement in ASAS health index with secukinumab 150 mg compared to placebo at Week 8.
Proportion of patients achieving an improvement in ASAS health index in each treatment arm at Week 24.	Proportion of patients achieving an improvement in ASAS health index in each treatment arm at Week 24.
ASAS health index at Week 8 and Week 24.	Mean ASAS health index score in each treatment arm at Week 8 and Week 24
Change from baseline in total spinal pain NRS score at all time points.	Total spinal pain NRS score in each treatment arm at all time points.
Change from baseline in total BASDAI score at all time points.	Total BASDAI score in each treatment arm at all time points.
ASDAS-CRP at Week 8 and Week 24.	Mean ASDAS-CRP in each treatment arm at Week 8 and Week 24.
[redacted]	[redacted]
Safety and tolerability of secukinumab 150 mg and 300 mg over the study period.	Safety and tolerability, as measured by frequency and severity of adverse events and changes in laboratory values of interest for secukinumab 150 mg and placebo (Baseline to Week 8) and for secukinumab 150 mg and 300 mg (Week 8 to Week 24).

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis and/or by the designated CRO (clinical research organization). 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).

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.

The two-sided p-values and confidence interval (CI) will be presented.

Data analyses will be presented by treatment group for both period I and period II separately. Efficacy and safety data for the placebo-controlled period I will be presented by the following 2 treatment groups of A and B whereas for period II the data will be presented for 5 treatment groups A1, A2, A3, B1 and B2.

The analysis will be conducted on all patients' data at the time the trial ends (Week 24).

Comparative efficacy data

Comparative efficacy analyses (i.e. inferential efficacy comparisons with placebo) will focus on the Treatment Period 1, when active drug and the placebo are given in a manner suitable for making comparisons (i.e., first 8 weeks of treatment). Comparative efficacy will be performed based on the FAS-TP1 population using the randomized treatment for Treatment Period 1. After week 8 till week 24, the efficacy endpoints will be summarized descriptively or otherwise specified using inferential analysis, on the FAS population using the randomized/re-assigned treatment for Treatment Period 2.

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 an 8-week placebo-controlled, double-blind treatment period starting from baseline till Week 8. Assessments of Week 8 are included in TP1 whereas administration of study drug at week 8 will be a part of TP2. Week 8 is the last visit of TP1 for all assessments except drug intake.

Treatment Period 2 is a 16 week double-blinded, active treatment period starting from Week 8 till Week 24 for administration of study drug. Week 8 assessments are considered as the baseline values for assessments during TP2.

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 24 weeks. For this study, the treatment phase consists of 8 weeks of on-treatment for period I (for treatment group A or group B) for secukinumab or placebo respectively, and 16 weeks of on-treatment for period II (for treatment group A1, A2, A3, B1 and B2) for secukinumab with 150 mg or 300 mg.

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 are created in SAP 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*	
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 72-113
Week 20	20	141	Day 114-151
Week 24	24	162	>=152 Days

* 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 primary endpoint analysis, data will be considered as Week 8 data, if Week 8 dose administration was done on or after the assessment date.

For parameters, which are not collected at every visit (e.g., FACIT-Fatigue©, ASAS Health Index), visit windows defined in Table 2-1 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 113 (combining Week 1 to Week 12 visit windows), Week 24 will extend from Day 114 to >=152 days (combining Week 20 to Week 24). If more than one assessment falls into the interval, the rules defined in Section 2.1.3 below are applied.

Table 2-2a Assessment windows for scheduled visits of Exposure Data

The administration of study drug at week 16 is not in relation to a study visit. For exposure data, a specific assessment window for week 16 is used in order to account for the home administration at week 16.

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	>= 128 Days

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 2-1).

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. spinal pain NRS response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

Table 2-3 Rules for selecting values for analysis

Timing of measurement	Type of data	Rule
Baseline	All data	See Section 2.1 Data analysis general information
Post-baseline efficacy	All data	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 study:

The **Enrolled Set** will include all patients, who provided informed consent.

The **Randomized Set** will consist of all patients, who were randomized into this study at Baseline. Mis-randomized patients will not be included in this analysis set.

The **Safety Set for Treatment Period 1 (SAF-TP1)** will consist of all patients, who received at least 1 dose of study treatment during this treatment period. Data will be analyzed according to the treatment actually received.

The **Safety Set for Treatment Period 2 (SAF-TP2)** will consist of all patients, who received at least 1 dose of study treatment during this treatment period. Data will be analyzed according to the treatment actually received.

The **Safety set (SAF)** will consists of all patients, who received at least one dose of study treatment. To analyze entire study period safety assessments, this dataset will be used.

The **Full Analysis Set for Treatment Period 1 (FAS-TP1)** will consist of all patients, who were randomized into this study at Baseline and received at least 1 dose of study treatment during this treatment period. Data will be analyzed according to the treatment assigned at randomization.

The **Full Analysis Set for Treatment Period 2 (FAS-TP2)** will consist of all patients, who were re-randomized or re-assigned at Visit 7 (Week 8) and received at least 1 dose of study treatment during this treatment period. Data will be analyzed according to the treatment assigned at randomization.

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 8 and Week 24), if appropriate, for each treatment group and all patients.

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 (<=30, >30-<55 and >=55)
- Sex
- Race
- Ethnicity
- Source of patient referral

Baseline disease characteristics will also be summarized for the following variables:

- History of axSpA including time (months) since first diagnosis of axSpA, time since first signs and symptoms, previous treatments of axSpA and reasons for discontinuation of these treatments.
- Smoking status at baseline
- HLA-B27 status [redacted]
- Spinal pain assessment on NRS, BASDAI, PASS, ASDAS, Patient's global assessment of disease activity, FACIT-Fatigue© and ASAS health index.

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.

Baseline disease characteristics QuantiFERON TB-Gold test and electrocardiogram related results will be listed only.

2.3.3 Medical history

Relevant medical history and current medical conditions will be summarized by system organ classes (SOC) and preferred terms (PT) of the latest version of MedDRA dictionary. Other relevant baseline information will be listed and summarized using descriptive statistics, as appropriate.

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) for each treatment period.

Treatment group for period I:

- Group A: AIN457 150 mg
- Group B: Placebo

Treatment group for period II:

- Arm A1: AIN457 150 mg
- Arm A2: AIN457 150 mg
- Arm A3: AIN457 300 mg
- Arm B1: AIN457 150 mg
- Arm B2: AIN457 300 mg

The analysis of study treatment data will be based on the safety set for period I, period II and the entire treatment period separately. The number of active and placebo injections will be summarized by treatment group up to Week 8, the number of double blind injections will be summarized by treatment group from Week 8 to Week 24.

Rescue medication

Not applicable.

Duration of exposure

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number and percentage of patients with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

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

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

Compliance

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.

Compliance (%) = 100(total no of injections administered)/ (no. of injections prescribed).*

Compliance for entire treatment period will be based on active treatment exposure.

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 spondyloarthritis 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).

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

2.5 Analysis of the primary objective

The primary objective is to assess the superiority of secukinumab 150 mg compared to placebo in achieving a spinal pain score < 4 on a 0-10 NRS at Week 8.

2.5.1 Primary endpoint

The primary efficacy endpoint is the proportion of patients with a response of spinal pain NRS score < 4 in secukinumab 150 mg s.c. and placebo at Week 8.

The analysis of the primary variable will be based on the FAS-TP1 patients.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis to be rejected is that the odds of response at Week 8 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 8 are higher under secukinumab compared to placebo.

Let pj denote the proportion of responders at Week 8 for treatment group j, j=0, 1, where

- 0 corresponds to placebo
- 1 corresponds to secukinumab

In statistical terms, the following hypothesis will be tested:

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

In other words,

HA: The odds ratio of achieving a response at Week 8 for secukinumab vs. placebo is different from 1.

The primary analyses will be conducted via logistic regression model with treatment, country and the stratification factor of prior exposure to TNF inhibitors (naïve/ inadequate responders to TNFα inhibitors) as factor. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab 150 mg treatment group to placebo group at Week 8.

The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is < 0.05; however, superiority of secukinumab will be claimed only if the direction is correct, i.e. if the odds of response are larger under secukinumab.

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

Grouping of countries: Due to the small number of subjects in some of the countries, the below mentioned countries will be grouped together to perform inferential analysis. The basis of grouping is a similar medical practice and geographical proximity in these countries:

1) Ireland & Great Britain
2) Italy, Spain & Croatia
3) Switzerland & Belgium
4) Finland & Sweden
5) Lithuania, Latvia & Estonia

If the grouping of countries does not allow proper analysis and if there are any challenges in model convergence, covariate "country" will be excluded from model.

2.5.3 Handling of missing values/censoring/discontinuations

If a patient has no value at Week 8, the missing value will be imputed as non-responders.

Average NRS spinal pain score will be calculated only if total and nocturnal pain score are non-missing.

2.5.4 Sensitivity analyses

The average spinal pain and raw (total and nocturnal spinal pain separately) NRS scores will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will include the same factors as the logistic model of primary analysis plus the respective baseline score as a covariate. Analysis visit will be used as repeat factor.

2.6 Analysis of the key secondary objective

There is no key secondary objective.

2.7 Analysis of secondary efficacy objective(s)

The secondary objective is to assess the proportion of patients with a BASDAI score < 4 at Week 8 of secukinumab 150 mg compared to placebo. The secondary endpoint will be analyzed analogous to the primary endpoint. The secondary endpoint will be included in a confirmatory testing strategy, it will be tested hierarchically after the primary endpoint.

2.7.1 Secondary endpoints

The secondary efficacy endpoint is the proportion of patients with a response of BASDAI score < 4 in secukinumab 150 mg and placebo at Week 8.

The analysis of the secondary variable will be based on the FAS-TP1 patients.

2.7.2 Statistical hypothesis, model, and method of analysis

The statistical hypothesis for BASDAI score < 4 being tested is that the odds of response at Week 8 are equal in the secukinumab 150 mg treatment group versus placebo group.

Let pj denote the proportion of responders at Week 8 for treatment group j, j=0, 1, where

- 0 corresponds to placebo
- corresponds to secukinumab

In statistical terms, the following hypothesis will be tested:

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

In other words,

HA: The odds ratio of achieving a response at Week 8 for secukinumab vs. placebo is different from 1.

The secondary analyses will be conducted analogous to the primary analyses, i.e., via logistic regression model with treatment, country and the stratification factor of prior exposure to TNF inhibitors (naïve/ inadequate responders to TNFα inhibitors) as factor. The Odds ratio, 95% confidence interval (CI) and p-value will be presented comparing secukinumab 150 mg treatment group to placebo group at Week 8. Confirmatory evidence for the superiority of secukinumab with respect to the secondary endpoint will be claimed only if the 2-sided p-value from the logistic regression model for the factor “treatment” is < 0.05 and if the direction is correct, i.e. if the odds of response are larger under secukinumab and if the superiority of secukinumab with respect to the primary endpoint has already been demonstrated.

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

2.7.3 Handling of missing values/censoring/discontinuations

If a patient has no value at Week 8, the missing value will be imputed as non-responders.
BASDAI score will be calculated based on the average of the non-missing answers available.

2.8 Safety analyses

All the safety analysis will be performed on the Safety Sets for period I and period II separately and also for entire treatment period, where applicable. Summaries will be performed separately for period I (from baseline to Week 8) and period II (from dosing at Week 8 to Week 24).

The safety follow-up will be carried forward until 12 weeks after the last study treatment. The analyses of the follow-up period will be consolidated to summaries for treatment-emergent adverse events, and serious adverse events to Treatment Period 2.

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 received erroneously at least once, the wrong treatment (not the correct one at randomization) an additional AE listing will be prepared displaying which events occurred after the treatment errors and the relationship with study drug.

2.8.1 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only the ***treatment-emergent*** AEs i.e. events that 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 until 12 weeks after last dose of study treatment.

The treatment-emergent adverse events will be summarized by system organ class and preferred term, severity (mild, moderate, severe), type of adverse event, relation to study treatment. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

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

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

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

For calculating the frequencies, 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 following adverse event summaries will be produced by treatment for Safety Set:

- Adverse events (overall and severe), regardless of study drug relationship by primary system organ class and preferred term
- Adverse events, regardless of study drug relationship by primary system organ class and preferred term and severity
- Adverse events (overall and severe), with suspected study drug relationship by primary system organ class and by preferred term
- Serious adverse events (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events (overall and severe), with suspected study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring additional therapy (overall and severe), regardless of study drug relationship, by primary system organ class and preferred term
- Deaths by primary system organ class and preferred term.
- Non-serious adverse events with a frequency greater than 2% regardless of study drug relationship, by primary system organ class and preferred term (for the legal requirements of ClinicalTrials.gov and EudraCT)

The crude rates of treatment-emergent adverse events 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 at the preferred term level for all SAEs and the common AEs (defined as with a frequency greater than 2%). A graphical display of the crude rates and exposure-adjusted incidence rates will be presented for all AEs and SAEs by SOC.

Exposure-adjusted AE incidence is defined as:

(Number of patients with new or worsened treatment emergent AEs) / (Total number of days a patient is on treatment summed over all patient/365.25)

The logic for calculation of the duration on treatment for a patient for exposure- adjusted AE at week x is as follows.

1) For treatment period 1 related reports:

If event occurred till week x: Duration=AE start date- date of first dose on study treatment +1

If event did not occur till week x: Duration= date of week x- date of first dose on study treatment +1

2) For entire treatment period related reports:

Please do not consider the duration when the subject is on placebo.

If event occurred till week x: Duration=AE start date- date of first dose on active study treatment +1

If event did not occur till week x: Duration= date of week x- date of first dose on active study treatment +1.

2.8.1.1 Adverse events of special interest / grouping of AEs

The following Safety Topic of Interest will be used to define adverse events of special interest (AESI):

- 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 "
- Hypersensitivity and injection site reaction: identified per SMQ (Standardized MedDRA Query) "Hypersensitivity"

For "Infections and infestations", please follow below table:

Safety Topic Of Interest (AESI)	SOC	Data Domain	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier
Tinea pedis	Infections and infestations	MEDDRA	10043873	Tinea pedis	PT	
Oral herpes	Infections and infestations	MEDDRA	10067152	Oral herpes	PT	
Oral candidiasis	Infections and infestations	MEDDRA	10030963	Oral candidiasis	PT	
Infections (Staphylococcal)	Infections and infestations	MEDDRA	10041925	Staphylococcal infections	HLT	
Infections (Skin structure)	Infections and infestations	MEDDRA	90000542	Infections of skin structures [STANDARD] (NMQ)	NMQ1	
Infections (Oesophageal candidiasis) (narrow)	Infections and infestations	MEDDRA	90000882	Oesophageal candidiasis	NMQ1	NARROW

				[STANDARD] (NMQ)		
Infections (Mycobacterial)	Infections and infestations	MEDDRA	10028440	Mycobacterial infectious disorders	HLGT	
Infections (Herpes viral)	Infections and infestations	MEDDRA	10019972	Herpes viral infections	HLT	
Infections (Fungal)	Infections and infestations	MEDDRA	10017528	Fungal infectious disorders	HLGT	
Infections (Central nervous system infections and inflammations)	Infections and infestations	MEDDRA	10007951	Central nervous system infections and inflammations	HLGT	
Infections (Opportunistic)	Infections and infestations	MEDDRA	90000701	Opportunistic infections [FINGOLIMOD] (CMQ)	NMQ1	
Infections (Oesophageal candidiasis) (broad)	Infections and infestations	MEDDRA	90000882	Oesophageal candidiasis [STANDARD] (NMQ)	NMQ1	BROAD
Infections (Infectious pneumonia)	Infections and infestations	MEDDRA	90000161	Infectious pneumonia [STANDARD] (NMQ)	NMQ1	BROAD
Infections	Infections and infestations	MEDDRA	10021881	Infections and infestations	SOC	
Candida infections	Infections and infestations	MEDDRA	10007134	Candida infections	HLT	

Above AESI will be considered and the number of patients with at least one event in each AESI grouping will be reported. Such AESI grouping consist of adverse events, for which there is a specific clinical interest in connection with secukinumab, or adverse events, which are similar in nature (although not identical).

All AESI groupings are defined through the use of PT, high level terms (HLT), SOC, SMQ, NMQ or through a combination of these components.

The AESI search table will be used to map reported adverse events to the notable adverse events groupings. The list of adverse events of special interest may be updated during the course of the trial based on accumulating safety data. Therefore, the clinical study report will list the AE groupings used and provide a listing of the corresponding AESI search table.

The crude rates of adverse events of special interest 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 at the preferred term level to adjust for differences in exposure. A graphical display of the crude rates and exposure-adjusted incidence rates will be presented for all AESIs by SOC.

Note that certain adverse events may be reported within multiple groupings.

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).

For urinalysis, only data listing 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.

Table 2.8-1 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.

Listing will be provided for all renal events captured in the study.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

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 2.8-2 below.

Table 2.8-2 Criteria for notable vital sign abnormalities

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

2.9 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 the FAS-TP1 and FAS-TP2 population at (Baseline to Week 8) and (Week 8 to Week 24) respectively.

FACIT-Fatigue© score

- Change from baseline in FACIT-Fatigue© score for each treatment group at Week 8.
- Change from baseline in FACIT-Fatigue© score for each treatment group at Week 24.
- Change from Week 8 in FACIT-Fatigue© score for each treatment group at Week 24.

All FACIT scales are scored so that a high score is good.

To achieve this, we reverse response scores on negatively-phrased questions. The total score is then calculated as the sum of the un-weighted subscale scores.

Calculate the score only if at least 11 questions are answered.

Calculate the total score as mentioned in below table:

Item Number	Reverse Item?		Item Response	Item Score
1	4	-		=
2	4	-		=
3	4	-		=
4	4	-		=
5	4	-		=
6	4	-		=
7	0	+		=
8	0	+		=
9	4	-		=
10	4	-		=
11	4	-		=
12	4	-		=
13	4	-		=

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____

Patient Accepted Symptoms State

- Proportion of patients in each treatment group with satisfactory PASS at Week 1, 2, 3, 4 and 8.
- Proportion of patients in each treatment group with satisfactory PASS at Week 12, 20 and 24.

ASAS Health Index

- Proportion of patients in each treatment group of achieving a minimal improvement (MCII) in ASAS health index at Week 8.
- Proportion of patients in each treatment group of achieving a minimal improvement (MCII) in ASAS health index at Week 24.

- Proportion of patients in each treatment group of achieving a significant improvement (SCI) in ASAS health index at Week 8.
- Proportion of patients in each treatment group of achieving a significant improvement (SCI) in ASAS health index at Week 24.
- Change from baseline in ASAS health index for each treatment group at Week 8 and Week 24.

Total Score calculation:

Total Score will be analyzed, if no more than 20% of data is missing. The total score is calculated as follows for respondents with one to a maximum of three missing responses

Sumscore={x/(N-m)}*N

Where

x= Item summation score

N=Total no of items applicable (Items "I have lost interest in sex." and "I have difficulty operating the pedals in my car" can be not applicable for few patients).

m=Number of missing Items

The definition of improvement is as follows:

- MCII (minimal clinically important improvement) ≥ 1 point of decrease from previous ASAS HI measurement
- SCI (Significant clinically improvement) ≥ 4 points of decrease from previous ASAS HI measurement

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

All the exploratory efficacy evaluation will be performed on FAS-TP1 and FAS-TP2 population based on the corresponding treatment periods. Refer to Table 1.2-1 of Section 1 for the list of exploratory endpoints.

The following exploratory efficacy variables will be analyzed on the FAS-TP1 and FAS-TP2 population at (Baseline to Week 8) and (Week 8 to Week 24) respectively for all applicable analysis visits unless otherwise specified.

- Spinal pain score: Average NRS spinal pain score will be calculated only if total and nocturnal pain score are non-missing.
- BASDAI score: It will be calculated based on the average of the non-missing answers available.
- ASDAS CRP
- Patient reported outcomes: FACIT-Fatigue©, PASS, ASAS health index

- The average and raw (total and nocturnal) spinal pain NRS scores will be analyzed using a repeated measures analysis of variance (ANOVA) model with treatment, country and the stratification factor of prior exposure to TNF inhibitors (naïve/ inadequate responders to TNFα inhibitors) as factors and respective baseline NRS score as covariate. The least squares means of the two treatment groups, least squares mean difference and 95% confidence interval for the difference in the two treatment groups will be presented along with the p-value based on the fitted linear model.
- Formula for ASDAS-CRP calculation: ASDAS (CRP) = 0.121 x total back pain + 0,110 x patient global + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579 x LN (CRP+1)

  The parameters, which are taken from patient reported outcomes, are expected to have values 0-10. CRP needs to be in the unit mg/L.

All endpoints relating to exploratory objectives will be summarized descriptively. Summary statistics will include relative and absolute frequencies for the categorical variables and the number of patients (n), minimum, mean, median and maximum for continuous variables will be separately provided for both period I and period II. Time courses of response rates and mean NRS-scores will be displayed graphically.

The following categorical exploratory endpoints will also be summarized categorically as absolute and relative frequencies (proportions, %). Any improvement or reduction is referred to as 'response' for all the below mentioned endpoints.

- Proportion of patients in each treatment group with response in spinal pain score < 4 at Week 1, 2, 3 and 4.
- Proportion of patients in each treatment group with response in spinal pain score < 4 at Week 24.
- Proportion of patients in each treatment group with response in BASDAI score < 4 at Week 24.
- Proportion of patients in each treatment group with response in ASDAS score < 2.1 at Week 8 and Week 24.
- Proportion of patients in each treatment group with response in ASDAS score < 1.3 at Week 8 and Week 24.
- Proportion of patients in Arm 1 with spinal pain score > 6 at Week 12 or Week 24.
- Proportion of patients achieving a spinal pain score < 4 for TNF-naïve patients compared to TNFα-inadequate responder (TNFα-IR) patients at Week 8 and Week 24.
- Proportion of patients with response in spinal pain score < 4 to secukinumab 150 mg at Week 8 maintaining a response at Week 24. Only descriptive statistics will be presented for this endpoint.

The statistical significance of the above endpoints between groups will be analyzed by 95% CI of proportion. P-value will be added if there are enough number of patients available.
The following continuous exploratory endpoints will also be summarized descriptively with number of patients (n), minimum, mean, standard deviation, median and maximum.

- Change from baseline in spinal pain score according to previous exposure to tumor necrosis factor (TNF) blockers at Week 1, 2, 3, 4, 8, 12 and 24.
- Change from baseline in total spinal pain score at all time points by each treatment group for each treatment period.
- Change from baseline in total BASDAI score at all time points by each treatment group for each treatment period.
- Change from baseline in ASDAS-CRP at Week 8 and Week 24.

If for a significant number of patients, the assignment to responder and / or non-responder status is incorrect, then a risk analysis may be performed.

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

To assess the assumed effect size at Week 8, a 43.6% response rate (spinal pain NRS < 4) is assumed for the secukinumab 150 mg group. This number is derived as an average of the response rates observed in the CAIN457F2320 and CAIN457F2310 studies (Baeten et al 2015). For the placebo group, a response rate at Week 8 of 23.5% (NRS < 4) was selected as assessed in the CAIN457F2320 study. This intermediate scenario takes into consideration a certain likelihood of a relatively high placebo response also in line with data from the TNFα reference studies and the CAIN457F2305 study in addition to the slightly milder course of the disease in the studied population (Baeten et al 2015).

Assuming conservatively a response rate of 23.5% in the placebo group and a response rate of 43.6% under secukinumab 150 mg, 332 patients in total (i.e. 249 patients in secukinumab 150 mg group and 83 patients in placebo group) would be needed under 3:1 (secukinumab: placebo) allocation to achieve 90% power on a (2-sided) 5% significance level. To compensate for drop-out patients or those with protocol deviations, a total of 352 patients (264 in secukinumab 150 mg group and 88 in the placebo group) should be recruited.

4 Change to protocol specified analyses

None.

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 Concomitant medication date imputation

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

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

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

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

Table 5.1-3: CMD date imputation

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

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

CM end date imputation

1. 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 will be set to NULL.

2. Else, if the CM end date month is missing, the imputed end date will be set to the earliest of the (Last contact date of subject in study, 31DECYYYY, date of death).

3. If the CM end date day is missing, the imputed end date will be set to the earliest of the (Last contact date of subject in study, last day of the month, date of death).

4. If the imputed CM end date is less than the existing CM start date, the CM start date will be used as the imputed CM end date.

5.1.3.1 Prior therapies date imputation

Not applicable

5.1.3.2 Post therapies date imputation

Not applicable

5.1.4 Medical History date of diagnosis imputation

Completely missing 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

5.2 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 models

5.4.1 Primary analysis

The null hypothesis to be rejected is that the odds of response at Week 8 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 8 are higher under secukinumab compared to placebo.

The primary analyses will be conducted via logistic regression model with treatment, country and the stratification factor of prior exposure to TNF inhibitors (naïve/ inadequate responders to TNFα inhibitors) 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 8.

SAS Code for logistic model

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

In cases where separation is a concern for the primary endpoint at Week 8, 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 COUNTRY STRATA;
Exact TRT / estimate=both;
Ods output exactoddsratio=exactoddsratio;
Run;
```

In addition to that the above analysis will also be performed a sensitivity analysis for raw spinal pain NRS score.

Mixed Model Repeated Measures (MMRM)

The following MMRM (or repeated measures ANOVA) model will be used for analysis of raw (total & nocturnal) and average spinal pain NRS score:

```
proc mixed data=.... order=internal;
where vis_1n in (2, 3, 4, 5, 6, 7);
class trt country strata;
model val_1n = trt bsval_1n country strata/ddfm=kr;
repeated vis_1n / subject=sid1a type=un;
lsmeans trt/ cl diff;
```

run;

If type=Unstructured (un) fails, we will use Compound Symmetry (cs)

5.4.2 Key secondary analysis

Not applicable

5.5 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
INCL01A	ICF is not signed or missing date of signing ICF	EXCLUDE FROM FAS and SAF	3
INCL01B	ICF date is after visit or assessment date	EXCLUDE FROM FAS	1
INCL01C	Patient unable to understand and communicate with the investigator	EXCLUDE FROM FAS	1
INCL02A	Pregnant or lactating female patients	INCLUDE IN EVERYTHING	0
INCL02B	Age is less than 18 years	EXCLUDE FROM FAS	1
INCL02C	Subject is not diagnosed with axSpA (either AS or nr-axSpA) according to ASAS axSpA classification criteria	INCLUDE IN EVERYTHING	0
INCL02D	Subject with back pain for less than 3 months and/or age on onset at or greater than 45 years.	INCLUDE IN EVERYTHING	0
INCL03	Active axSpA as assessed by BASDAI, BASDAI score is less than 4 or missing at baseline	INCLUDE IN EVERYTHING	0
INCL04	Spinal pain NRS score equal or less than 4 at Baseline	INCLUDE IN EVERYTHING	0
INCL05	Patients do not have at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks in total prior to randomization	INCLUDE IN EVERYTHING	0
INCL06	Patients who are regularly taking NSAIDs as part of their axSpA therapy are not on stable dose for at least 2 weeks before randomization	INCLUDE IN EVERYTHING	0
INCL07	Patients who have previously been on a TNFalpha inhibitor with no appropriate wash-out period prior to randomization	INCLUDE IN EVERYTHING	0
EXCL01	Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL02	Previous treatment with prohibited medication not washed out appropriately before randomization	INCLUDE IN EVERYTHING	0
EXCL03	Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor	INCLUDE IN EVERYTHING	0
EXCL04	Patient used investigational drug or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug	INCLUDE IN EVERYTHING	0
EXCL05	Subject with history of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes	INCLUDE IN EVERYTHING	0
EXCL06	Patients previously treated with any biological immunomodulating agents, except those targeting TNFalpha	INCLUDE IN EVERYTHING	0
EXCL07	Patients who have been exposed to more than one anti-tumor necrosis factor alpha (anti- TNFalpha) agent	INCLUDE IN EVERYTHING	0
EXCL08	Patients with previous treatment with any cell depleting therapies including but not limited to anti-CD20 or investigational agents	INCLUDE IN EVERYTHING	0
EXCL09	Pregnant or nursing (lactating) women, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test	INCLUDE IN EVERYTHING	0
EXCL10	Women of childbearing potential, not using effective methods of contraception during the entire study	INCLUDE IN EVERYTHING	0
EXCL11	Patients with active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy	INCLUDE IN EVERYTHING	0
EXCL12	Patients with other ongoing mechanical diseases affecting the spine that may confound evaluation of the benefit of secukinumab therapy	INCLUDE IN EVERYTHING	0
EXCL13	Patients with underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which immunocompromise the patient.	INCLUDE IN EVERYTHING	0
EXCL14	Patients with significant medical problems or diseases	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
EXCL15	Patients with history of clinically significant liver disease or liver injury as indicated by abnormal liver function tests	INCLUDE IN EVERYTHING	0
EXCL16	Patients with history of renal trauma, glomerulonephritis, or patients with one kidney only, or an exceeding serum creatinine level	INCLUDE IN EVERYTHING	0
EXCL17	Patients with abnormal total white blood cell count or platelets or neutrophils or hemoglobin at screening	INCLUDE IN EVERYTHING	0
EXCL18	Active systemic infections during the last 2 weeks prior to randomization (exception: common cold)	INCLUDE IN EVERYTHING	0
EXCL19	Patients with history of ongoing, chronic or recurrent infectious disease or evidence of active tuberculosis infection.	INCLUDE IN EVERYTHING	0
EXCL20	Patients with known infection with human immunodeficiency virus, hepatitis B or hepatitis C at screening or randomization	INCLUDE IN EVERYTHING	0
EXCL21	Patients with history of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years	INCLUDE IN EVERYTHING	0
EXCL22	Patients with any current severe progressive or uncontrolled disease	INCLUDE IN EVERYTHING	0
EXCL23	Patients with any medical or psychiatric condition, which would preclude the participant from adhering to the study protocol.	INCLUDE IN EVERYTHING	0
EXCL24	Patients with history or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization	INCLUDE IN EVERYTHING	0
EXCL25	Patients with administration of live vaccines 6 weeks prior to randomization or plans for administration of live vaccines during the study period	INCLUDE IN EVERYTHING	0
OTH01	Pregnancy test not performed as required per protocol	INCLUDE IN EVERYTHING	0
OTH02	Spinal pain NRS score at week 8 is missing.	INCLUDE IN EVERYTHING	0
OTH03	Spinal pain NRS score at baseline is missing	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
OTH04	Patient PRO data was not collected according to the protocol	INCLUDE IN EVERYTHING	0
WITH01	Pregnant patient not withdrawn from study	INCLUDE IN EVERYTHING	0
WITH02	ICF withdrawn but patient continuing in the study	INCLUDE IN EVERYTHING	0
TRT01	Dosing error in comparative dosing phase (too many injections in treatment phase 1 and 2)	INCLUDE IN EVERYTHING	0
TRT02	Dosing error in comparative dosing phase (less than 2 injections in treatment phase 2)	INCLUDE IN EVERYTHING	0
TRT03	No study medication administered.	INCLUDE IN EVERYTHING	0
TRT04	Patient randomized mistakenly in the study and did not receive study drug.	EXCLUDE FROM FAS and SAF	3
TRT05	The patient was re-randomized to the wrong treatment arm.	INCLUDE IN EVERYTHING	0
TRT06	Patient was randomized to the wrong stratum at baseline.	INCLUDE IN EVERYTHING	0
TRT07	Study medication was administered, which could have been damaged.	INCLUDE IN EVERYTHING	0
COMD01	Prohibited medication consumed during study.	INCLUDE IN EVERYTHING	0
COMD02	Painkillers intake during 24h before a visit involving a disease activity assessment.	INCLUDE IN EVERYTHING	0

Table 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

Table 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

6 Reference

Baeten D, Sieper J, Braun J et al; MEASURE 1 Study Group; MEASURE 2 Study Group (2015) Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Eng J Med; 376(26):2534-48