NOVARTIS

Clinical Development

CAIN457/Secukinumab/Cosentyx®

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A randomized, double-blind, placebo controlled, multicenter, phase III study of subcutaneous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in Chinese participants with active non-radiographic axial spondyloarthritis

Statistical Analysis Plan (SAP) Amendment 2

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	Prior to DBL	Amendment 1	Revised the baseline value definition	2.1.1.3 Screening, baseline and post-baseline definitions
	Prior to DBL	Amendment 1	Clarified the subgroup of interest	2.2.1 Subgroup of interest
	Prior to DBL	Amendment 1	Moved the original sensitivity analyses to supportive analyses. Removed non-parametric regression for ASAS40	2.5.4 Supportive analyses
	Prior to DBL	Amendment 1	Clarified of the analyses of SF-36 PCS	2.6.2 Statistical hypothesis, model, and method of analysis
	Prior to DBL	Amendment 1	Corrected the CTCAE version from 4.0 to 4.03	2.7.3 Laboratory data
	Prior to DBL	Amendment 1	Change the definition of ASAS20 in case baseline evaluation equal to 0 and the percentage of worsening does not exist	5.1 Description of efficacy variables
	Prior to DBL	Amendment 1	Corrected the Newcombe Confidence interval expression	5.5.2.1 Crude incidence and 100*(1-α)% confidence interval
8th Jan 2025	Prior to Week 52 DBL	Amendment 2	Clarified the analyses window of Week 60 visit	2.4.1.1 Visit window
	Prior to Week 52 DBL	Amendment 2	Added the rule for post-baseline safety by-visit summary when there are multiple assessments with the same time of completion	2.4.1.2 Multiple assessments within visit windows
	Prior to Week 52 DBL	Amendment 2	Updated the retrieving rule of safety topics of interest	2.7.1.1 Adverse events of special interest / grouping of AEs

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse Event
ALT	Alanine Aminotransferase / Glutamic Pyruvic Transaminase / GPT
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society criteria
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST	Aspartate Aminotransferase / Glutamic Oxaloacetic Transaminase / GOT
ASQoL	Ankylosing Spondylitis Quality of Life Questionnaire
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
[redacted]	[redacted]
BSL	Baseline
cDMARD	conventional (i.e., non-biologic) DMARD
CPO	Country Pharma Organization
CRF	Case Report Form
CRP (hsCRP)	(high sensitivity) C-Reactive Protein
CRP+	hsCRP > ULN (as defined by the central lab)
CSR	Clinical Study Report
DMARD	Disease Modifying Antirheumatic Drug
DMC	Data Monitoring Committee
DMS	Document Management System
ECG	Electrocardiogram
eCRF	electronic Case Report/Record Form
EMA / EMEA	European Medicines (Evaluation) Agency
[redacted]	[redacted]
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
HLA	Human Leukocyte Antigen
IA	Interim Analyses
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
MAR	Missing At Random
[redacted]	[redacted]
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Multiple Imputation
MMRM	Mixed Model Repeated Measures
MNAR	MRI
MRI	Magnetic Resonance Imaging
MRI+	Positive for sacroiliitis (active inflammatory lesions)

MTX	Methotrexate
nr-axSpA	Non-radiographic axial SpondyloArthritis
NRI	Non-Responder Imputation
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCS	Physical Compnent Summary
PD	Pharmacodynamic
PG	Pharmacogenetic
PK	Pharmacokinetics
PoC	Proof of Concept
PRN	According to need, as required
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PsA	Psoriatic Arthritis
QoL	Quality of Life
RA	Rheumatoid Arthritis
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
s.c.	Subcutaneous(ly)
SCR	Screening
SF-36	Medical Outcome Short Form (36) Health Survey
SpA	Spondyloarthritis
TFLs	Tables, Figures, Listings
TNF	Tumor Necrosis Factor
TNF-IR	TNFα Inhibitor Incomplete Responders
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organization

1 Introduction

Data will be analyzed by Novartis according to this SAP and the data analysis Section 12 of the clinical study protocol. The 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.

1.1 Study design

This is a randomized, double-blind, placebo-controlled study of secukinumab 150 mg s.c. to evaluate the safety, tolerability, and efficacy in Chinese participants with active non-radiographic axial spondyloarthritis (nr-axSpA).

A screening period of up to 10 weeks before randomization will assess participant eligibility, followed by 16 weeks of double-blind treatment period and 44 weeks open label period.

Approximately 134 participants will be randomized in a ratio of 1:1 to receive secukinumab 150 mg s.c. or placebo:

- Group 1: secukinumab 150 mg (1mL, 150 mg/mL) s.c. pre-filled syringe (PFS) at baseline (BSL), Weeks 1, 2, and 3, followed by administration every four weeks starting at Week 4
- Group 2: placebo (1 mL) s.c. PFS at BSL, Week 1, 2 and 3, followed by administration every four weeks starting at Week 4

Participants will be stratified at randomization according to the subgroup of objective sign of inflammation they belong to (based on their CRP and MRI status at screening: CRP+ and MRI+, CRP+ and MRI-, CRP- and MRI+).

Additionally, it is planned to enroll no more than approximately 10% Tumor Necrosis Factor – Inadequate Response (TNFα-IR) participants in the study.

The primary analysis will be performed after all participants complete Week 16 visit to support registration in China.

From Week 16, all participants will switch to open label secukinumab 150 mg s.c., including all placebo participants. The first dose of open label secukinumab 150 mg s.c. should start at the Week 16 visit, only after performing all assessments for that visit. However, all participants and investigators/site staff will remain blinded to the original randomized treatment group assignment (150 mg vs placebo).

At Week 24, non-responders (defined as not achieving ASAS20) will be escalated to secukinumab 300 mg s.c. Responders will continue secukinumab 150 mg s.c. treatment.

Study treatment will continue up to Week 48.

At end of treatment visit will be performed 4 weeks after last study treatment administration i.e. at Week 52 and a post treatment follow-up visit is to be done 12 weeks after last study treatment administration for all participants (regardless of whether they complete the entire study as planned or exit the study early).

A primary endpoint analysis will be conducted after all participants complete Week 16 visit. The final analysis will be conducted on all participant data at the time the study ends.

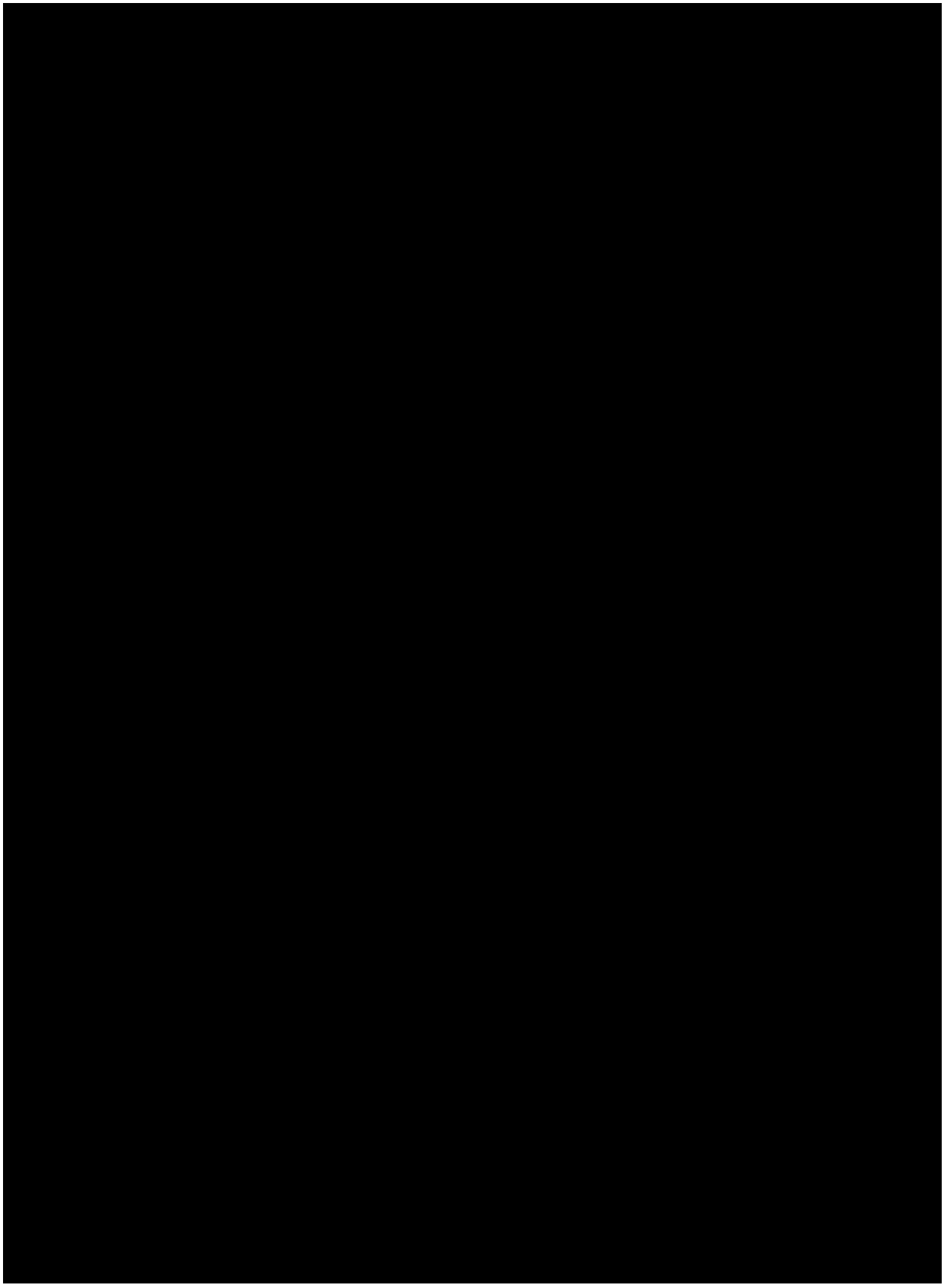
Interim analysis is not applicable in this study.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of TNF-α naive patients achieving an ASAS40 response (Assessment of SpondyloArthritis International Society criteria).	• ASAS40 response rate at Week 16 ASAS40 response is defined as an improvement of ≥40% and an absolute improvement from baseline of ≥2 units on a 10-point scale in at least three of the four main domains and no worsening assessed at all in the remaining domain. Main ASAS domains: 1. Patient's global assessment of disease activity measured on a VAS scale 2. Patient's assessment of back pain, 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. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of overall patients achieving an ASAS40 response.	• ASAS40 response rate in overall patients at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of patients meeting the ASAS 5/6 response criteria.	• ASAS 5/6 response rate at Week 16 ASAS 5/6 response is defined as an improvement of ≥20% in at least five of all six domains.
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).	• Change from baseline in total BASDAI at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of patients achieving BASDAI 50.	• BASDAI 50 proportion at Week 16 BASDAI 50 is defined as an improvement of at least 50% in the BASDAI total score compared to baseline.

Objective(s)	Endpoint(s)
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline of high sensitivity C-Reactive Protein (hsCRP).	• Change from baseline in hsCRP at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in total Bath Ankylosing Spondylitis Functional Index (BASFI).	• Change from baseline in BASFI at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in sacroiliac (SI) joint edema on MRI.	• Change from baseline in SI joint edema score on MRI at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of subjects achieving an ASAS20 response.	• ASAS20 response rate at Week 16 ASAS20 response is defined as an improvement of ≥20% and an absolute improvement from baseline of ≥1 unit on a 10-point scale in at least three of the four main domains and no worsening of ≥20% and ≥1 unit at all in the remaining domain.
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in Short Form-36 Physical Component Summary (SF-36 PCS).	• Change from baseline in SF-36 PCS at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores.	• Change from baseline in ASQoL score at Week 16
• To assess the efficacy of secukinumab 150 mg s.c. relative to placebo at Week 16 based on the proportion of patients achieving ASAS partial remission.	• ASAS partial remission rate at Week 16 ASAS partial remission is defined as a value not above 2 units in each of the four main ASAS domains on a 10-point scale.
• To evaluate overall safety and tolerability of secukinumab.	• Number of participants with adverse events (AE) serious adverse events (SAE), clinically significant changes in laboratory value and vital signs.



2 Statistical methods

2.1 Data analysis general information

The primary endpoint analysis will be performed after all participants complete Week 16 or discontinued earlier and the final analysis will be conducted on all participant data at the time the study ends, both by Novartis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Novartis will perform the analysis at Week 16 and final analysis. Statistical software SAS version 9.4 or later will be used.

Summary statistics for continuous variables will generally include the number of participants (N), minimum, lower quartile, mean, standard deviation (SD), median, upper quartile, and maximum. For binary or discrete variables, the absolute number of participants in each category and relative frequencies will be provided.

Unless otherwise specified, two-sided 95% confidence intervals will be displayed.

In case of a global health disruptive event, such as pandemic/epidemic (e.g., COVID-19), affecting the ability of the patient or the site to adhere to protocol requirements and assessments and therefore leading to a potential increase in the number of missing measurements, additional analysis populations may be defined as per the instructions and procedures outlined in Section 16.9 in the protocol.

The efficacy evaluation of secukinumab relative to placebo will generally focus on the first 16 weeks of treatment unless otherwise specified.

Data analysis will be presented by treatment group. Efficacy and safety data for the 16-week placebo-controlled period and the entire treatment period as appropriate will be presented by the following two treatment groups. Participants may be included in more than one treatment group for some analysis (e.g. exposure adjusted adverse events over the entire treatment period).

These treatment groups represent the regimens to which participants will be eligible to be randomized:

- Secukinumab 150 mg regimen
- Placebo regimen

Note that the treatment groups above for a participant may differ depending on the time period of the analysis and whether one assesses the participant for efficacy or safety.

Data may also be presented after Week 16, by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the participants experience over the course of the entire trial. (e.g., placebo participants who are reassigned to secukinumab 150 mg, non-responders who are escalated to secukinumab 300 mg).

All listings will be presented by treatment sequence.

2.1.1 General definitions

2.1.1.1 Treatment groups

The summaries by treatment will be performed by the randomized treatment or treatment sequence.

- Randomized treatment:
    - AIN457 150 mg s.c.
    - Placebo s.c.
- Treatment sequence:
    - AIN457 150 mg
    - AIN457 150 mg –AIN457 300 mg
    - Placebo
    - Placebo – AIN457 150 mg
    - Placebo – AIN457 150 mg – AIN457 300 mg

For some safety summaries (e.g. exposure-adjusted) the 'switch' treatment may be summarized separately:

Week 1 – Week 16: AIN457 150 mg, Placebo

Entire study: Any AIN457 150 mg, Any AIN457 300 mg, Any AIN457, Placebo

Unless otherwise specified, at the primary endpoint analysis, efficacy data for the placebo-controlled period and safety data up to Week 16 and Entire study will be presented. Additional aspects of efficacy, safety and tolerability of secukinumab will be investigated in the final analysis. Additional analyses may also be performed to support interactions with health authorities, as necessary.

2.1.1.2 Study Day 1 and other study days

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

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

The descriptor "Day 0" will not be used.

2.1.1.3 Screening, baseline and post-baseline definitions

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

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. However, for vital sign, laboratory assessments and ECG if no pre-treatment value exists, values obtained after first dose of treatment can be used as baseline only if it was collected on the same day as first dose.

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

2.1.1.4 Day of last dose of randomized study treatment

The date of last dose will be collected via the electronic case report form (eCRF). The subject's exposure will be calculated considering the end of study visit (e.g., study completion visit). If a subject discontinued early, then the last dose + 84 days or the last visit during the follow-up period whichever occurs earlier is considered.

2.2 Analysis sets

The following analysis sets will be used in this study:

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

Mis-randomized participants are defined as those participants 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 participants are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all participants from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, participants will be evaluated according to the treatment assigned to at randomization, but actual stratum, if stratified randomization is used.

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

2.2.1 Subgroup of interest

The primary endpoint will be evaluated within TNFα naïve patients using the stratification subgroups (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+). The analysis will be performed using a logistic regression model as specified in Section 5.5.1.1.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of participants screened will be presented. In addition, the reasons for screen failures will be provided. The number and percentage of participants in the randomized set who completed the study periods and who discontinued from treatment or study prematurely (including the reason for discontinuation) will be presented at the end of each treatment period (e.g. Week 16, and entire treatment period), if appropriate, for each treatment group and all participants.

For each protocol deviation (PD), the number and percentage of participants for whom the PD applies will be tabulated by initial randomized treatment groups on the Randomized set population.

2.3.2 Demographics and baseline characteristics

The following common background and demographic variables will be summarized:

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI) = (body weight in kilograms) / (height in meters)^2

Categorical variables:

- Age categories (<45 years, 45 years and older)
- Gender
- Race
- Ethnicity
- Smoking status at baseline

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

- Participant's global assessment of disease activity and other ASAS components, hsCRP (mg/L and > ULN), ESR (mm/h), prior use (yes/no) of TNF-α inhibitors, use (yes/no) and separate NSAIDs (yes/no) and dose of concomitant NSAIDs, MTX (yes/no) and MTX (mg/week), susulfasalazine (yes/no) and sulfasalazine (g/day) and systemic corticosteroids (yes/no) and systemic corticosteroids (mg/day) at randomization, time since first diagnosis of nr-axSpA and time since onset of inflammatory back pain(years), HLA-B27, [redacted], total back pain (VAS), nocturnal back pain (VAS), total BASDAI score, spinal pain (BASDAI question #2), total BASFI score, [redacted], and each randomization strata level (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+).

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

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

2.3.3 Medical history

A history of nr-axSpA with focus on previous extra-articular involvement and past therapies for nr-axSpA will be obtained and summarized by treatment group for all patients in the randomized set. Any other significant prior or active medical condition at the time of signing informed consent will be recorded and coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

To establish a BSL level of cardiovascular risk, the number and percentage of participants with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each participant has will also be summarized by treatment group. If it is unknown whether a participant currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that participant.

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

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

2.4.1 Study treatment / compliance

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

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of participants 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 is defined as the time from first dose of study treatment to the time of treatment switch (for participants who switch treatment) or minimum of (last dose of the treatment + 84 days) and (last visit date). Participants who switch treatment during the study (e.g. from placebo to active treatment) will have exposure to both medications using the appropriate start and stop dates.

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

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

The analysis of duration of exposure described above will be done for the entire study treatment period.

2.4.1.1 Visit window

Analysis visit windows will be used for the data that is summarized by visit; they are based on the study visit and evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are protocol defined scheduled visits around which analysis visit windows were created to cover the complete range of days within the study.

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, 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.

As for the Week 60 (follow-up) visit, only assessments that come as nominal Week 60 visit will be directly assigned as Analysis Week 60 visit. Other assessments that are beyond the last on-treatment visit window (Week 52) won't be mapped to any analysis visit. Of note, subjects are allowed to have gaps in visits.

Table 2-1 Analysis visit windows

Analysis visit	Target Day	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Baseline	1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 1	≤ 7
Week 1	8	2-11	2-11				
Week 2	15	12-18	12-22				
Week 3	22	19-25					

Week 4	29	26-43	23-57				
Week 8	57	44-71		2-85	2-85		
Week 12	85	72-99	58-99				
Week 16	113	100-127	100-155	86-141	86-239	2-239	8-239
Week 20	141	128-155					
Week 24	169	156-183	156-169	142-225			
Week 28	197	184-211	170-239				
Week 32	225	212-239					
Week 36	253	240-267					
Week 40	281	268-295	240-323	226-323			
Week 44	309	296-323					
Week 48	337	324-351					
Week 52	365	352-379	324-379	268-379	240-435	240-379	240-435

*The first administration of randomized study treatment (first dose) is defined as Day 1.
Group 1: Patient's global assessment of disease activity (VAS), Patient's assessment of back pain intensity (VAS), BASFI, BASDAI, [redacted], hsCRP, Vital signs
Group 2: Hematology, blood chemistry, urinalysis
Group 3: ASQoL, SF-36, [redacted]
Group 4: Lipids
Group 5: Weight, ECG
Group 6: MRI

The following rules are used to determine the window for an applicable visit post baseline "Lower limit"="upper limit of prior applicable visit"+1. "Upper limit"="target day of current visit"+ integer part of ("target day of next applicable visit"-"target day of current visit")/2. Lower limit of the first applicable visit is always Day 2. Day 1 is the date of the first dose of randomized study treatment.

The mapping described above applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. If more than one assessment falls into the interval, the rules defined in Section 2.4.1.2 are applied.

The analysis visit will be used for listing of visit and period for safety data. If a visit falls after the last visit window, it is not assigned an analysis visit and will be listed under label "After Week 60".

2.4.1.2 Multiple assessments within visit windows

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

The definition of baseline assessment is included in Section 2.1.1.3. For post-baseline visit windows the following applies (unless otherwise specified):

- for *quantitative variables*, the *closest* to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen),

- for *qualitative variables*, the *worst* record is selected. It is noted that in the analyses performed, *worst* case is always well defined (e.g., for urine protein values "+" and "++", the worst case is defined as "++"),
- in case qualitative variables are based on quantitative variables, e.g. BASDAI50, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

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

Timing of measurement	Type of data	Rule
Baseline	All data	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 data/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. For MRI, a baseline value is the last measurement prior to dosing if available. Otherwise, take the first value within 7 days post dosing.
Post-baseline efficacy	All data	For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used. For visits during which the patient switchers from placebo to AIN the following will be done based on whether the patient met the rescue criteria: a. if the analysis visit window is <= week 16, then - if available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo) - if there are no data on or before the switch then the closest measurement to the target date after the switch will be used b. if the analysis visit window is > week 16, then - if available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN) - if there are no data AFTER the switch then the closest measurement to the target date before the switch 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
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	For visits without switch of treatment in the window, the measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used. For visits during which the patient switchers from placebo to AIN the following will be done based on whether the patient met the rescue criteria: a. if the analysis visit window is <= week 16, then - if available, the closest measurement to the target date which is ON or BEFORE the switch date will be used (i.e. the closest measurement to target which is on placebo) - if there are no data on or before the switch then the closest measurement to the target date after the switch will be used b. if the analysis visit window is > week 16, then - if available, the closest measurement to the target date which is AFTER the switch date will be used (i.e. the closest measurement to target which is on AIN) - if there are no data AFTER the switch then the closest measurement to the target date before the switch 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 and differs, the earliest measurement will be used; * if time of completion is the same, the measurements will be averaged; * if time does not exist the measurement from the lowest CRF visit number will be used.
Post-baseline safety	Notable abnormalities (e.g. lab)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be summarized in separate tables by treatment group. Concomitant treatments will be displayed by study period as appropriate.

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 within 84 days after the last dose will be a concomitant medication, including those which were started pre-BSL 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 participants 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 non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

Prior surgeries and procedures are defined as surgeries and procedures done prior to first dose of study treatment. Any surgeries and procedures done between the day of first dose of study treatment and within 84 days after the last dose will be a concomitant surgeries and procedures, including those which were started pre-BSL and continued into the period where study treatment is administered.

The number and percentage of participants receiving prior and concomitant nr-axSpA 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 nr-axSpA therapies previously. The use of NSAIDs, systemic corticosteroids and DMARD (MTX, Leflunomide, sulfasalazine) use will 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.

2.5 Analysis of the primary objective

The primary objective of this study is to assess the efficacy of secukinumab relative to placebo at week 16 based on the proportion of participants achieving an ASAS40 response in TNF-α naïve participants. The consistency of the treatment difference between this bridging study and the global study will be evaluated.

2.5.1 Primary endpoint

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 16 in TNF-α naïve participants with active nr-axSpA. The analysis of the primary variable will be based on the FAS participants.

The clinical question of interest is: What is the effect of secukinumab 150 mg s.c. versus placebo on ASAS40 response after 16 week-treatment in Chinese patients with active nr-axSpA who are TNF-α naïve?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The primary estimand is described by the following attributes:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted nr-axSpA population

B. Variable: composite of remaining in the study and on randomized treatment through 16 weeks and achieving ASAS40 response at Week 16

C. Treatment of interest: Secukinumab 150 mg s.c. and Placebo

D. Intercurrent event: the intercurrent event of discontinuation from treatment or study prior to Week 16 has been addressed via the variable definition

E. Population-level summary: difference in proportions of responders between secukinumab 150 mg and placebo groups

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be conducted via logistic regression with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate. Difference in marginal response proportions between secukinumab regimen and placebo regimen and the corresponding 95% confidence interval (CI) will be computed utilizing the logistic regression model fitted.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS40 response for data up to Week 16 will be handled as follows:

1. Participants who discontinue from treatment or study for any reason will be considered as non-responders from the time of discontinuation through Week 16

2. Participants who do not have the required data to compute responses (i.e., ASAS components) at BSL and at the specific timepoint will be classified as non-responders at the specific timepoint.

Participants who are unblinded prior to the scheduled time point will be considered non-responders from the time of unblinding up to Week 16.

The primary analysis will use the non-responder imputation.

[redacted]

2.6 Analysis of the secondary objective

2.6.1 Secondary endpoint

The secondary efficacy variables are described below. Secondary efficacy variables will be analyzed using the FAS population.

- ASAS40 at Week 16
- ASAS 5/6 at Week16
- BASDAI at Week 16
- BASDAI50 at Week 16
- hsCRP at Week 16
- BASFI at Week 16
- SI joint edema on MRI at Week 16
- ASAS20 at Week 16
- SF-36 PCS at Week 16
- ASQoL at Week 16
- ASAS partial remission at Week 16

The clinical questions of interest are:

- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS 40 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS 5/6 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in BASDAI at Week 16 in Chinese participants with active nr-axSpA had patients completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint BASDAI 50 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in hsCRP at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in BASFI at Week 16 in Chinese participants with active nr-axSpA had patients completed 16 weeks-treatment?

- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in SI joint edema on MRI at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 week-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS20 response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in SF-36 PCS at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the change from baseline in ASQoL at Week 16 in Chinese participants with active nr-axSpA had participants completed 16 weeks-treatment?
- What is the effect of secukinumab 150 mg s.c. versus placebo on the composite endpoint ASAS partial remission response at Week 16 and the completion of 16 weeks-treatment in Chinese participants with active nr-axSpA?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered without dose changes.

The estimand definition of all secondary binary variables (e.g., ASAS 5/6, etc.) will have the same attributes as that for the primary estimand, except for the variable of interest.

Estimand definition for the secondary continuous variables (e.g., BASDAI change from baseline, etc.) is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted nr-axSpA population

B. Variable: change from baseline in the variable of interest

C: Treatment of interest: Secukinumab 150 mg s.c and Placebo

D. Intercurrent event: discontinuation from treatment or study prior to Week 16

E. Population-level summary: difference in variable means between Secukinumab 150 mg and Placebo groups

2.6.2 Statistical hypothesis, model, and method of analysis

ASAS40 at Week 16

The proportion of patients meeting the response criteria will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate.

ASAS 5/6 at Week 16

The proportion of participants meeting the response criteria will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate.

BASDAI at Week 16

Between-treatment differences in the change from baseline in BASDAI will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and analysis visit as factors and baseline BASDAI score and weight as continuous covariates. Treatment by analysis visit and baseline BASDAI score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

BASDAI50 at Week 16

The proportion of participants meeting the response criteria at Week 16 will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and baseline weight and baseline BASDAI score as covariates.

hsCRP at Week 16

For the change in hsCRP, since evidence from the literature would suggest that the data are not normally distributed (Huffman et al. 2006), analysis will be performed on the $\log_e$ ratio of the treatment value vs baseline value (calculated by dividing the post-baseline value by the baseline value and then applying the $\log_e$ transformation) to normalize the distribution of hsCRP at each analysis visit. Between-treatment differences in the change in hsCRP relative to baseline will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and analysis visit as factors and $\log_e$ baseline hsCRP and weight as continuous covariates. Treatment by analysis visit and $\log_e$ baseline hsCRP by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The estimate and the 2-sided 95% confidence intervals obtained from the model will be back transformed to the original scale.

BASFI at Week 16

Between-treatment differences in the change from baseline in BASFI will be evaluated using MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and analysis visit as factors and baseline BASFI score and weight as continuous covariates. Treatment by analysis visit and baseline BASFI score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

SI joint edema on MRI at Week 16

The change from baseline to Week 16 in inflammation measured by SI joint total edema score will be evaluated using an ANCOVA model with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors, and weight and baseline inflammation score as covariates. Missing data will be imputed using multiple imputation prior to running ANCOVA.

ASAS20 at Week 16

The proportion of participants meeting the response criteria will be evaluated using a logistic regression model with treatment group and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate.

SF-36 PCS at Week 16

Between-treatment differences in the change from BSL in SF36-PCS summary score will be evaluated using a MMRM with treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and analysis visit as factors and baseline SF-36 PCS score and weight as covariates. Treatment by analysis visit and baseline SF-36 PCS score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

ASQoL at Week 16

Summary statistics of observed data by visit and change from baseline in ASQoL will be provided for each treatment regimen. Between-treatment differences will be evaluated using MMRM. Treatment group, stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) and analysis visit will be included as categorical factors and baseline ASQoL scores and weight as continuous covariates. Treatment by analysis visit and baseline ASQoL scores by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model.

ASAS partial remission at Week 16

Response at Week 16 to ASAS partial remission criteria will be evaluated using a logistic regression model with treatment and stratification factor (CRP+/MRI+, CRP+/MRI-, CRP-/MRI+) as factors and weight as a covariate.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data for binary efficacy variables (e.g., ASAS5/6, etc.) for data up to Week 16 will be handled as follows:

1. participants who discontinue from treatment or study for any reason will be considered as non-responders from the time of discontinuation through Week 16

2. participants who do not have the required data to compute responses (i.e., ASAS components) at BSL and at the specific timepoint will be classified as non-responders at the specific timepoint.

Participants who are unblinded prior to the scheduled time point will be considered non-responders from the time of unblinding up to Week 16.

Continuous variables (e.g., BASDAI change from baseline, etc.) will be analyzed using a mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption. For analyses of these parameters, if all post-BSL values are missing then these missing values will not be imputed and this participant will be removed from the analysis

of the corresponding variable, i.e., it might be that the number of participants providing data to an analysis is smaller than the number of participants in the FAS.

For SI joint edema on MRI, a multiple imputation approach will be applied to handle missing data.

2.7 Safety analyses

The analysis of safety data by treatment may be provided for each Treatment Period separately and all periods combined, as appropriate. The analysis of safety data will be conducted on the Safety Set, which includes subjects who receive any study treatment. Safety analysis 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 subjects who received not the treatment assigned at randomization, 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.

The safety variables to be analyzed include Adverse events (AEs), clinical laboratory tests (hematology, chemistry and urinalysis), physical examination results, ECGs, and deaths. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

2.7.1 Adverse events (AEs)

The crude incidence of treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized by primary system organ class and preferred term. Confidence intervals for the crude rate will be derived as described in Section 5.5.2. In addition, exposure time-adjusted incidence rates including 95% confidence intervals will be provided for the entire treatment period (See Section 5.5.3). A graphical display of the crude incidence rates and exposure-adjusted rates will be presented for all AEs and serious AEs by system organ class.

Adverse events reported will be presented in descending frequency according to its incidence in total secukinumab group (combining all secukinumab treatment groups) starting from the most common event. Summaries (crude incidences only) will also be presented for AEs by severity and for study treatment related AEs. If a particular AE ‘severity’ is missing, this variable will be listed as missing and treated as missing in summaries. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

Adverse events will also be reported separately by Standardized MedDRA Query (SMQ) according to MedDRA. The MedDRA version 26.1 will be used for reporting. Non-treatment emergent adverse events will be listed.

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

The safety analysis that will be performed for treatment emergent AEs and on treatment labs and vital signs for each analysis period is described in Table 2-3.

Algorithms for date imputations will be provided in Programming Datasets Specification.

Table 2-3 Overview of analysis on some safety endpoints

Analysis period	AEs & SAEs	AEs-SMQ	AEs by severity	study drug related AEs	Notables for (vitals/ ECG), lab criteria	Risk
Day 1 – Week 16	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence
Entire Treatment	• crude incidence • exp.time adjusted incidence	• exp.time adjusted incidence	• crude incidence	• crude incidence	• crude incidence	• crude incidence • exp.time adjusted incidence

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

- At the PSOC for AE and SAE
- At the PT level for common AEs, which is defined as at least 2% of the patients in the secukinumab during the initial treatment period (i.e. up to week 16) or events that had an incidence rate of at least 5.0 cases per 100 subject-years in the combined secukinumab groups during the entire treatment period
- At Level 1 for Risks and SMQ analyses

2.7.1.1 Adverse events of special interest / grouping of AEs

Safety topics of interest, including risks defined in the Risk Management Plan (RMP) or other topics of interest for signal detection or routine safety analysis can be retrieved via the RMP flag and SPP flag. The crude incidence and exposure-adjusted incidence rates for the safety topics of interest will be summarized.

2.7.2 Deaths

Separate summaries will be provided for deaths.

2.7.3 Laboratory data

The summary of lab data will only include treatment emergent data, which are defined as those lab assessments after the first dose of study treatment and on or before last dose +84 days.

Reported laboratory assessments with either a less than or greater than sign (“<” or “>”) will be used for analysis after removal of the sign and conversion to standard unit. These laboratory data will be displayed in listings using the standard unit with the reported sign (“<”or “>”).

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

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 test group, laboratory test and treatment group. Change from baseline will only be summarized for participants with both baseline and post baseline 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 evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a participant'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 the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline. 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: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl trasferase (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 2-4 CTCAE grades for laboratory parameters to be analyzed

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L	Life-threatening consequences; urgent intervention
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased*	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x 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

CTCAE v4.03 Term	Grade 1	Grade 2	Grade 3	Grade 4
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 up to week 16 or entire) analyzed. Of note, baseline will be defined as last assessment prior to first dosing in initial treatment phase.

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
  - <0.8x LLN
- LDL, cholesterol, triglycerides:
  - >=UNL
  - >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 2-5:

Table 2-5 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN, >20xULN
AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN; >20xULN
TBL	>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 (Potential Hy’s Law)

Parameter	Criterion
	Note: elevated ALP may suggest obstruction as a consequence of gall bladder or bile duct disease; ALP may also be increased in malignancy. FDA therefore terms Hy's Law cases as indicators of pure hepatocellular injury. This does not mean that cases of ALT or AST >3xULN & TBL >2xULN & ALP ≥ 2xULN may not result in severe DILI.

Notes:
1) In studies which enroll subjects 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 listing may be provided for subjects with abnormal laboratory data. Data of subjects with newly occurring or worsening liver enzyme abnormalities may be listed in an additional listing.

The laboratory values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

The summary of ECG will only include treatment emergent data, which are defined as those ECG measurements after the first dose of study treatment and on or before last dose + 84 days.

Analysis in ECG parameters using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by ECG parameter and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

Change from baseline = post-BSL - BSL

The following quantitative variables will be summarized: ECG mean heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval (QTc). Fridericia (QTcF) corrections will be presented for QTc.

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

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

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

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

2.7.4.2 Vital signs

The summary of vital signs will only include on treatment data, which are defined as those vital sign measurements after the first dose of study treatment and on or before last dose + 84 days.

Analysis of the vital sign measurements using 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 participants with both baseline and post-baseline values and will be calculated as:

Change from BSL = post-BSL – BSL

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

Table 2-6 Criteria for notable vital sign abnormalities

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

2.10 Patient-reported outcomes

Patient reported outcomes will be evaluated based on FAS unless otherwise specified.

BASDAI

The following variables will be evaluated:

- BASDAI
- BASDAI50

See Section 2.6 and Section 2.12 for details.

BASFI

See Section 2.6 and Section 2.12 for details.

Patient's global assessment of disease activity (VAS)

See Section 2.12 for details.

Patient's assessment of back pain intensity (VAS)

See Section 2.12 for details.

SF-36

The following variables will be evaluated:

- SF-36 domain scores (based on a scale of 0-100)
- SF-36 PCS and MCS scores (norm-based scores)
- SF-36 PCS and MCS responder (improvement of ≥ 2.5 points, Lubeck, 2004)

See Section 2.6 and Section 2.12 for details.

While the SF-36 PCS score change from baseline is a secondary objective, the SF-36 MCS score, SF-36 domain scores and SF-36 PCS/MCS responder are not included in the objectives but will be presented as supportive information.

ASQoL

See Section 2.6 and Section 2.12 for details.

[redacted]

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

No interim analysis will be performed.

2.14 Primary endpoint analysis

The primary endpoint analysis will be performed after all participants have completed the Week 16 visit or have discontinued earlier. The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each participant received at randomization until after the final database lock. The primary endpoint analysis will be used for regulatory submission.

Subsequent to the primary endpoint analysis, the final analysis is planned after participants have completed the Week F60 assessments and may be used for regulatory submission and/or publication purposes. Additional analyses may be performed to support interactions with health authorities, as necessary.

3 Sample size calculation

3.1 Primary endpoint(s)

As it is a bridging study for China registration, this study will pursue an estimation strategy rather than formal hypothesis testing of treatment difference.

Analysis of the phase III study CAIN457H2315 with secukinumab in nr-axSpA showed a placebo response rate of about 29.2% and a secukinumab 150 mg response rate of 41.5% after 16 weeks for ASAS40 in TNF-α naïve participants. Assuming 10% of randomized participants will be TNF-α IR and 90% of randomized participants will be TNF-α naïve. With 134 participants, 120 of them are TNF-α naïve (1:1 ratio to two groups), then there are approximately 77.3% probability to show at least 50% global treatment difference (6.15%) and approximately 90.7% probability to show positive treatment difference.

Table 3-1 Probability of Success with Different Observed Response Rates of ASAS40 in TNF-α naïve participants

	Observed Response Rate				Criterion 1		Criterion 2	
	Secukinumab (p_1)	Placebo (p_2)	p_1-p_2	95% CI of (p1-p2)	Aimed Treatment Difference	PoS	Aimed Treatment Difference	PoS
Scenario 1	0.395	0.292	0.103	(-0.066, 0.272)	> 0.0615	0.699	> 0	0.864
Scenario 2	0.415	0.292	0.123	(-0.046, 0.293)	> 0.0615	0.773	> 0	0.907
Scenario 3	0.435	0.292	0.143	(-0.027, 0.313)	> 0.0615	0.835	> 0	0.939
Scenario 4	0.455	0.292	0.163	(-0.008, 0.334)	> 0.0615	0.885	> 0	0.962

4 Change to protocol specified analyses

[redacted]

[redacted]

Per protocol Section 12.4.4, ASAS40 response in active nr-axSpA participants at Week 16 was supposed to be evaluated using a non-parametric regression model as a "sensitivity analysis". This analysis has been removed (SAP Section 2.5.4), considering the non-parametric regression model will target the odds ratio, while the primary estimand targets the marginal difference as the summary measurement. Additionally, no evidence for lack of robustness was identified from the global pivotal study CAIN457H2315.

Per protocol Section 12.5.2, Qualitative changes of ECG were supposed to be summarized. But the qualitative changes (interpretation) of ECG were not collected in CRF and hence will not be analyzed (SAP Section 2.7.4.1).

5 Appendix

5.1 Description of efficacy variables

Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, 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. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

5. Spinal mobility represented by the BASMI lateral spinal flexion assessment
6. C-reactive protein (acute phase reactant)

ASAS Response Criteria-20% (ASAS20)

ASAS20 response is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain with non-zero baseline assessment, or no worsening of ≥1 unit on a scale of 10 in the remaining domain with zero baseline assessment.

ASAS Response Criteria-40% (ASAS40)

ASAS40 response is defined as an improvement of ≥40% and ≥2 units on a scale of 10 in at least three of the four main domains and no worsening at all in the remaining domain.

ASAS 5/6 improvement criteria

The ASAS 5/6 improvement is defined as an improvement of ≥20% in at least five of all six domains.

ASAS partial remission criteria

The ASAS partial remission criteria are defined as a value not above 2 units in each of the four main domains on a scale of 10.

ASAS components

Patient's global assessment of disease activity (VAS)

The patient's global assessment of disease activity will be performed using a 100 mm visual analog scale (VAS) ranging from not severe to very severe, after the question, *"How active was your disease on average during the last week?"*

Patient's assessment of total back pain and nocturnal back pain intensity (VAS)

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "*Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?*" and "*Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?*"

Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those participants with AS. The ten questions were chosen with a major input from participants with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the participants' ability to cope with everyday life. A 10 cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10. In the case that some of the BASFI questions are missing, then the average of the non-missing items is used (Braun 2009, van Tubergen 2001).

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 AS:

1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness
5. Morning stiffness severity
6. Morning stiffness duration

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness is taken and is then added to the sum of the first 4 questions. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good

candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 secs and 2 mins to complete. At least 4 questions should be non-missing to calculate the BASDAI score. Otherwise, BASDAI score will be missing (Haywood 2002). If both Q5 and Q6 are missing or one of Q1 to Q4 is missing, then the total sum should be divided by 4 instead of 5. If two of Q1 to Q4 is missing and both Q5 and Q6 are not missing, then the sum should be divided by 3.

[redacted]

High sensitivity C-reactive protein (hsCRP)

This assessment will be performed in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

Since the results of this test may unblind study personnel, results from the central lab will be provided for screening and baseline only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

[redacted]

[redacted]

Definition of Sacroiliitis on MRI

An MRI will be considered positive for sacroiliitis (active inflammatory lesions, "positive MRI", MRI+) if the following characteristics are evident (Sieper et al 2009):

- The presence of definite subchondral bone marrow oedema/osteitis highly suggestive of sacroiliitis is mandatory.
- The presence of synovitis, capsulitis, or enthesitis only without concomitant subchondral bone marrow oedema/osteitis is compatible with sacroiliitis but not sufficient for making a diagnosis of active sacroiliitis.

Amount of signal required: if there is one signal (lesion) only, this should be present on at least two slices. If there is more than one signal on a single slice, one slice may be enough.

[redacted]

[redacted]

[redacted]

[redacted]

5.2 Description of health-related quality of life variables

5.2.1 SF-36

The Short Form Health Survey (SF-36) is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales (domains) that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role- Emotional, and Mental Health. Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed. The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients. The eight domains are based on a scale from 0-100 while PCS and MCS are norm-based scores with a mean of 50 and a standard deviation of 10.

Quality metric uses weighted maximum likelihood estimation, a modified version of item response theory (IRT) to estimate scale scores when a respondent is missing multiple items. The PCS summary score measure requires scores for seven scales, one of which must be the PF scale and the MCS score also requires scores for seven scales, one of which must be the MH scale. Only one item is needed for each of the multi-item domains.

5.2.2 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL is a self-administered questionnaire designed to assess health-related quality of life in adult patients with Ankylosing Spondylitis. The ASQoL contains 18 items with a dichotomous yes/no response option. A single point is assigned for each "yes" response and no points for each "no" response resulting in overall scores that range from 0 (least severity) to 18 (highest severity). As such, lower score indicates better quality of life. Items include an assessment of mobility/energy, self-care and mood/emotion. The recall period is "at the moment," and the measure requires approximately 6 minutes to complete.

At least 15 answered questions are required to be able to calculate ASQoL using mean imputation, (sum of answered) / (number answered) * 18 (Doward 2003).

5.3 Imputation rules

5.3.1 Study drug

Any partial dates will be imputed as follows:

We take the earlier day of

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

5.3.2 AE date imputation

Impute AE end date:

1. If the AE end date 'month' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose data + 84 days), 31DECYYYY, date of death).
2. If the AE end date 'day' is missing, the imputed end date should be set to the earliest of the (min (last visit date, last dose date + 84 days), last day of the month, date of death)
3. If AE 'year' is missing or AE is ongoing, the end date will not be imputed.

Impute AE start date:

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

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

2. Else AE start reference date = treatment start date

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

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

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

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

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

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

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

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

a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

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

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

5.3.3 Concomitant medication date imputation

Impute CM end date:

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of treatment end date (date of the last dose) and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of treatment end date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

Impute CM start date:

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JULYYYY)
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY)
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:

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

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

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

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

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

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

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

5.3.3.1 Prior therapies date imputation

See Section 5.3.3

5.3.3.2 Post therapies date imputation

See Section 5.3.3

5.4 AEs coding/grading

Adverse events will also be coded according to MedDRA dictionary, using a narrow search. The MedDRA version used for reporting the adverse events will be described in a footnote. Safety topics of interest, such as risks defined in the Safety Profiling Plan, Risk Management Plan or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Sheet.

5.5 Statistical models

Primary analysis

This section provides the details of model stated in Section 2.5.

5.5.1.1 Logistic regression

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model with treatment as factor and weight as a covariate. The marginal standardization method will be used to calculate the mean response rate in each treatment group as well as their difference. This method uses the same fitted logistic model, but involves using the model to predict, for each patient in the study, the mean outcome assuming assignment to each particular treatment group in turn, assuming each patient's observed values for the other baseline covariates (i.e., weight). Averaging these predictions for each treatment group provides

the estimate of the mean response rate for each treatment group. Then the difference will be derived based on the estimated mean response rates comparing s.c. regimen vs. placebo.

SAS code example as the following,

options validvarname=v7;

%Margins(data = *mydata*,
class = *treatments strata*,
response = *AVAL*,
roptions = event = '1',
model = *treatment baseline_weight strata*,
dist = binomial,
margins = *treatment*,
options = cl diff)

If convergence is not obtained the following sequential steps will be used:

1. Remove *strata*. If still no convergence, perform exact test

When exact test is applied, the risk difference and confidence intervals will be estimated via PROC FREQ and EXACT statement.

Input dataset should only contain data from the two treatment groups to be compared.

5.5.1.2 Sensitivity analysis

5.5.1.2.1 Multiple imputation

Under MAR assumption

A linear regression model will be used to perform multiple imputation (MI) under a missing-at-random (MAR) assumption. To help preserve the relationship between outcome and covariates within each treatment a separate model will be run for each treatment. This will also help ensure that the imputation model does not make stronger assumptions on data relations than the analysis model.

The SAS code below outlines a template for the analysis where covariates and visits can be added or removed as required. To ensure that results can be replicated the data should be sorted by subject number before running the model (the data should be in horizontal format with one subject per dataset row).

proc mi data= seed=4572301 nimpte=100 out=*mi_out*;

by *treatment*;

class *strata*;

fcs reg (/details);

var *strata weight value1 value2 value3*;

run;

Where in the template code the continuous variable to be imputed is *value* (e.g. *value1* could be the baseline value and *value2* the first post-treatment measurement of the variable to be imputed.) Normally, all data collection visits during the analysis period of interest would be included in the model. Including variables using a CLASS statement instead of a BY statement should help facilitate model convergence also when the number of non-missing data points are low for some specific covariate level and visit combination. The FCS option is used to ensure that also non-monotone missing data can be handled in an appropriate way.

If convergence is not obtained the following sequential steps will be used:

1. Remove *weight*.

For a situation where several variables need to be imputed using separate models (e.g., using independent models to impute each component needed to derive a response variable *V*) a stepwise process needs to be implemented as outlined below:

1. Run the SAS code as described above for the first variable to be imputed
2. Run the SAS code as described above for the next variable to be imputed (but with the following changes: "data=*mi_out*", "out=*mi_out2*", "by *treatment _imputation_*", "nimpute=1")
3. Repeat step 2, but with input dataset equal to the output dataset from the prior step, until all *j* variables have been imputed resulting in a dataset named mi_out_j
4. Derive the variable *V* from within mi_out_j

The required analysis (e.g. ANCOVA) is then performed separately within each imputation dataset (as identified by variable *_imputation_*). To obtain the final result of the imputation process the analysis result from each imputation dataset needs to be combined according to Rubin's rule as outlined below:

ods output parameterestimates=*mi_result;*

proc mianalyze data=;

modeleffects *estimate*;

stderr *estimate_se*;

run;

The *estimate* and *estimate_se* parameters come from the analysis model used to analyze the imputed variable within each imputation dataset (e.g., from the lsmean estimate of the treatment difference and its standard error obtained from PROC LOGISTIC or PROC MIXED)

To obtain binary resonse rates and confidence intervals for individual treatment groups the following process should be followed (exemplified for one visit):

ods output binomialprop=*bin_est*;

proc freq data=;

by *treatment _imputation_;*

table *response* / binomial (cl=wilson correct);

run;

Then apply a logit transformation on the saved proportions and derive its standard error:

data *bin_est*; set *bin_est*;

estimate=log(*_bin_*/(1-*_bin_*));

estimate_se=*e_bin*/(*_bin_**(1-*_bin_*));

run;

The transformed binomial proportion estimates and its standard errors are then combined by applying Rubin's rules (Rubin, 1987) as described above using PROC MIANALYZE. Before presenting the combined data it needs to be transformed back as follows:

data *mi_result*; set *mi_result*;

prop_est=1/(1+exp(-*estimate*));

prop_lower=1/(1+exp(-*lclmean*));

prop_upper=1/(1+exp(-*uclmean*));

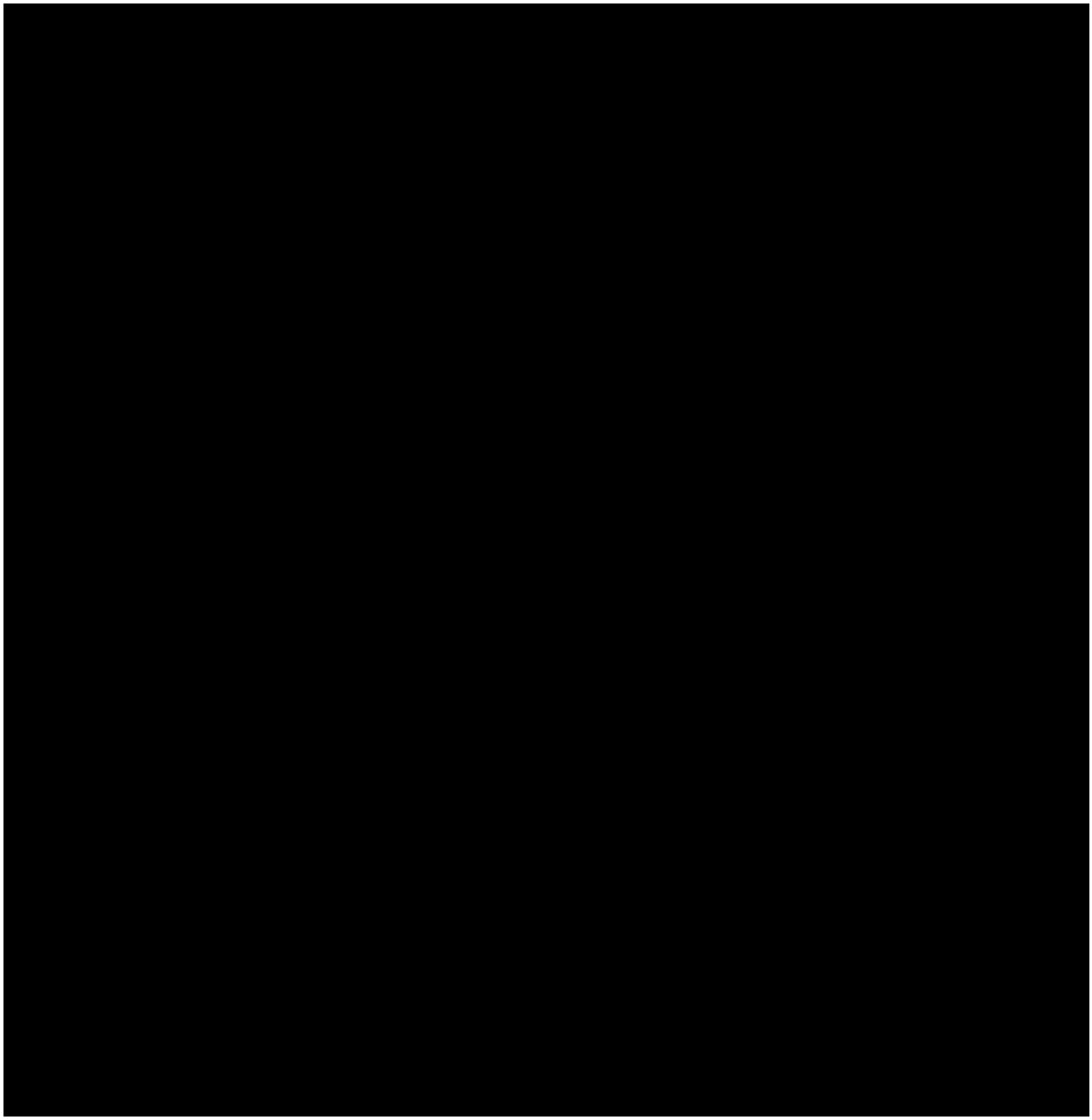
run;

If all responses are imputed the same as 0 (or 1) for all imputation datasets for a specific treatment or subgroup then the between-imputation-variation will be zero. The combined final response rate for the specific treatment or subgroup would be presented as seen in any of the imputed datasets together with 95% CI from Wilson's method (as obtained from PROC FREQ).

The following steps will be performed to handle special cases:

- If after imputation all responses (observed+imputed) are the same either 0 or 1 for all imputation datasets for a specific treatment or subgroup it will not be possible to perform a logit transformation and the response rate (0% or 100%) for these cases will be presented together with the 95% CI
- If after imputation the average response rate is the same across all imputed datasets (but not 0 or 1) there is no between dataset variation and Rubin's rules cannot be applied. Instead, the average response will be used with 95% CI from Wilson's method (as obtained from PROC FREQ)

[redacted]



Secondary analysis

5.5.1.4 Analysis of binary and categorical data

5.5.1.4.1 Summary statistics for binary and categorical data

Summary statistics for discrete variables will be presented in contingency tables and will include count and frequency in each category. If applicable, confidence intervals will be derived as well 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-α/2), n as total number of subjects (i.e. number of subjects in the denominator), p as estimated crude incidence (number of subjects with event / n) and p=1-q))

Then the lower limit is

$$L = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq + 1)}}{2(n + z^2)}\right)$$

And the upper limit is

$$U = 100 \times \min\left(0, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq - 1)}}{2(n + z^2)}\right)$$

In addition, if L>p then L=p and if U<p then U=p.

The placebo-adjusted response rates include 95% confidence interval will be derived using PROC FREQ with RISKDIFF statement. Note the response value should be sorted with '1' ahead of '0'. Fisher's exact test will be applied to rate events, pairwise treatment group comparisons to placebo to active controls (using PROC PREQ with FISHER statement). 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 analysis.

5.5.1.4.2 Logistic regression

Certain binary outcome variables, e.g. response outcomes, will be evaluated using a logistic regression model. The model will include factors and covariates as specified for respective analysis same as section 5.5.1.1.

5.5.1.5 Analysis of continuous data

5.5.1.5.1 Summary statistics for continuous data

Summary statistics (including N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum) will be provided for continuous data by visit and treatment group.

5.5.1.5.2 Analysis of covariance

An analysis of covariance (ANCOVA) model will be used to analyze some endpoints. The model will include factors and covariates as specified for respective analysis. The SAS code below outlines a template for the analysis where covariates can be added or removed as required:

ods output diffs=*lsm_diff* lsmeans=*lsm_est*;

proc mixed data=;

by *visit*;

class *treatment strata*;

model *outcome = treatment strata baseline_weight*;

lsmeans *treatment* /diff cl;

run;

Least-square-mean (LSM) estimated for each treatment group and LSM difference, confidence intervals and p-value for the difference between each dose of secukinumab and placebo, and between secukinumab doses if relevant, can be obtained.

5.5.1.5.3 Mixed-effects repeated measures model

Some endpoints will be analyzed using a longitudinal model that comprises several visits. The model used will be mixed model repeated measures (MMRM) with factors, covariates, interactions and covariance structure as specified for respective analysis. The SAS code below outlines a template for the analysis where covariates and interaction terms can be added or removed as required:

ods output diffs=*lsm_diff* lsmeans=*lsm_est*;

proc mixed data=;

class *treatment strata visit*;

model *outcome=treatment strata visit baseline weight treatment * visit*

*baseline * visit / ddfm=kr*;

repeated *visit* / type=un subject=;

lsmeans *treatment * visit* / diff cl;

run;

Least-square-mean (LSM) estimated for each treatment group and LSM difference, confidence intervals and p-value for the difference between each dose of secukinumab and placebo, and between secukinumab doses if relevant, can be obtained.

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

1. Change to ddfm=bw. If still no convergence, perform step 2.
2. Change to type=cs. If still no convergence, perform step 3.
3. Remove covariates in the following order until convergence: *weight, baseline*visit, strata*

5.5.2 Crude incidence and related risk estimates

5.5.2.1 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 $(1-\alpha/2)$-quantile of the standard normal distribution (SAS: z=PROBIT(1-α/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

$$\mathrm{L} = 100 \times \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - \frac{1}{n} + 4p(nq+1)}}{2(n+z^2)}\right)$$

And the upper limit is

$$\mathrm{U} = 100 \times \min\left(0, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - \frac{1}{n} + 4p(nq-1)}}{2(n+z^2)}\right)$$

In addition, if L > p then L = p and if U < p then U = p.

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 analysis.

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

For an investigational drug group with n_1 subjects at risk, independent from the control group (e.g., placebo or comparator) with n_0 subjects at risk, of whom x_1 and x_0 experience a certain event with probability π_1 and π_0 respectively, the odds ratio is estimated as $\frac{p_1/(1-p1)}{p_0/(1-p_0)}$ with $p_1 = x_1/n_1$ and $p_0 = x_0/n_0$. A conditional exact 100*(1-α)% confidence interval 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 LOGISTIC.

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

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

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

5.5.3 Exposure adjusted incidence rate and related risk estimates

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

It will be assumed that for each of n subjects in a clinical trial the time t_j $(j = 1,...,n)$ to the first occurrence of a centain 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 $\lambda = D/T$, where $T = \sum_{j=1}^{n} t_j$ and D is the number of subjects with at least one event. Conditionally on T, an exact 100*(1-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 $U = \frac{0.5c_{\alpha/2,2D+2}}{T}$

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 5-3 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)

6 References

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