NOVARTIS

Clinical Development

AIN457/Secukinumab

CAIN457HDE01 / NCT03906136

A randomized, open label multicenter trial to investigate the efficacy of a treat-to-target treatment strategy with secukinumab (AIN457) as a first-line biologic compared to a standard-of-care treatment over 36 weeks in patients with active axial spondyloarthritis (axSpA) – Ascalate

Statistical Analysis Plan (SAP)

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01-Apr-2021	Creation of amendment 1.0	Updated study design section for interim analysis	Section 1.1 Study design
		Updated general definitions section for start date and end date of SOC treatment	Section 2.1.1 General definitions
		Compliance section removed	Section 2.1.1 Compliance
07-Feb-2022	Creation of amendment 2.0	Dropped interim analysis section from study design	Section 1.1 Study design
		Updated analysis population for patient disposition	Section 2.3.1 Patient disposition
		Updated analysis population for protocol deviations	Section 2.3.2 Protocol deviations
		[redacted]	[redacted]
		Dropped sample size justification for interim analysis	Section 2.14 Interim analysis
		Removed rule of exclusion criteria of analysis sets	Section 5 Appendix
		Updated study treatment	Section 2.4.1 Study treatment
		Added definition of Enrolled set and dropped definition of per-protocol set	Section 2.2 Analysis set
		Added section for worsening clinically notable vital signs	Section 5.4 Clinically notable vital signs
		Additional information added forBASMI derivation	Section 2.7.1.8 BASMI
		Additional information added for vital sign	Section 2.8.4.2 Vital signs

Date	Reason for update	Outcome for update	Section and title impacted (Current)
27-May-2022	Creation of amendment 3.0	• Updated visit window for Week 12 • Updated ASDAS disease severity at Baseline • Updated prior, concomitant and non-drug therapies/procedures to include categories of medication [redacted]	• Section 2.1.2 Visit windows • Section 2.2.1 Subgroup and Section 2.5.4 Supportive • Section 2.4.2 Prior and concomitant medication, Section 5.3 Concomitant medication grouping and Section 5.6.1 SAS code [redacted]
03-July-2023	Creation of amendment 4.0	• Specify treatment periods • Minor corrections	• Section 2.1.1 definition treatment phase and Clarification SOC treatment • Section 2.4.1 Study Treatment • Section 2.5.1 primary endpoint, adapt ASAS 20 response to CSP [redacted] • Section 5.4 Clinically notable vital signs

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
ASAS	Ankylosing SpondyloArthritis International Society
ASAS-HI	ASAS health index
ASDAS	Ankylosing SpondyloArthritis disease activity score
ASQoL	Ankylosing spondylitis quality of life
AUC	Area Under the Curve
ATC	Anatomical Therapeutic Chemical
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
axSpA	Axial Spondyloarthritis
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis Metrology Index
bid	bis in diem/twice a day
BSL	Baseline
BMI	Body mass index
CM	Concomitant Medication
CI	Confidence Interval
CRF	Case Report Form
CRP	C-reactive protein
CRO	Contract Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Drug administration record
DMARD(s)	Disease-Modifying Anti-Rheumatic Drug(s)
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOT	End of treatment
ENR	Enrolled set
ESR	Erythrocyte sedimentation rate
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACIT	Functional assessment of chronic illness therapy
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
IA	Interim Analysis
ICF	International classification of functioning
IVR	Interactive Voice Response
IWR	Interactive Web Response
[redacted]	[redacted]

MCS	Mental component score
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed-Effect Model Repeated Measures
MRI	Magnetic resonance imaging
MTX	Methotrexate
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-Inflammatory Drug
nr-axSpA	Non-Radiographic Axial Spondyloarthritis
o.d.	Once Daily
OR	Odds Ratio
OS	Overall Survival
PCS	Physical component summary
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial remission
PRO	Patient-reported Outcomes
PT	Preferred Term
qd	Quaque die / once a day
QoL	Quality of Life
r-axSpA	Radiographic Axial Spondyloarthritis
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SF-36	Short form health survey
[redacted]	[redacted]
SOC	Standard-of-Care
TFLs	Tables, Figures, Listings
T2T	Treat-to-Target
[redacted]	[redacted]
TNFα	Tumor Necrosis Factor Alpha
VAS	Visual Analog Scale
WBCs	White blood cells
WHO	World Health Organization

1 Introduction

This document describes the detailed statistical methodology to be used in the phase IIIb Clinical Study Report (CSR) for the analysis of AScalate study CAIN457HDE01.

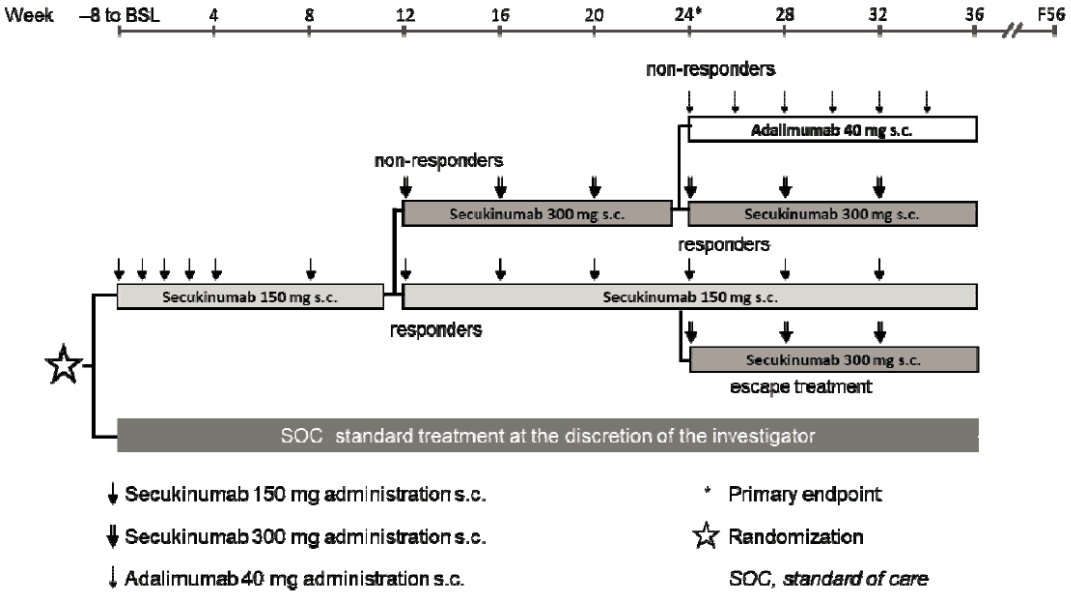
CSR deliverables (shells for tables, figures, listings) and further programming specifications are described in the Tables, Figures & Listings (TFL) shells and Programming Datasets Specifications (PDS) respectively.

Data will be analyzed by Novartis and/or the designated Contract Research Organization (CRO). Statistical software SAS version 9.4 or higher will be used for generating TFLs. The content of this statistical analysis plan (SAP) is based on the final study protocol (CAIN457HDE01 version 02 dated 17-May-2021). The planned analysis is described in Section 12 of the protocol.

1.1 Study design

This is a randomized, parallel-group, open-label, multicenter study in subjects with active axial spondyloarthritis (axSpA). The aim of the study is to demonstrate that the efficacy of a Treat-to-Target (T2T) approach (with secukinumab as a first-line biologic) is superior to a Standard-of-Care (SOC) approach in terms of achieving strong clinical efficacy in patients with active axSpA who are naïve to biological therapy and who have an inadequate response to prior non-steroidal anti-inflammatory drug (NSAID) treatment. The study will include an 8-week screening period, a 36-week treatment period, and a 20-week safety follow-up period. Neither investigators nor subjects will be blinded. The primary endpoint is the percentage of subjects achieving an Ankylosing SpondyloArthritis International Society (ASAS) 40% response (ASAS40) at Week 24. At Baseline, subjects will be randomized equally to one of 2 treatment groups (T2T or SOC); a total of 300 subjects (150 subjects in each arm) will be randomized as shown in Figure 1-1.

Figure 1-1 Study design



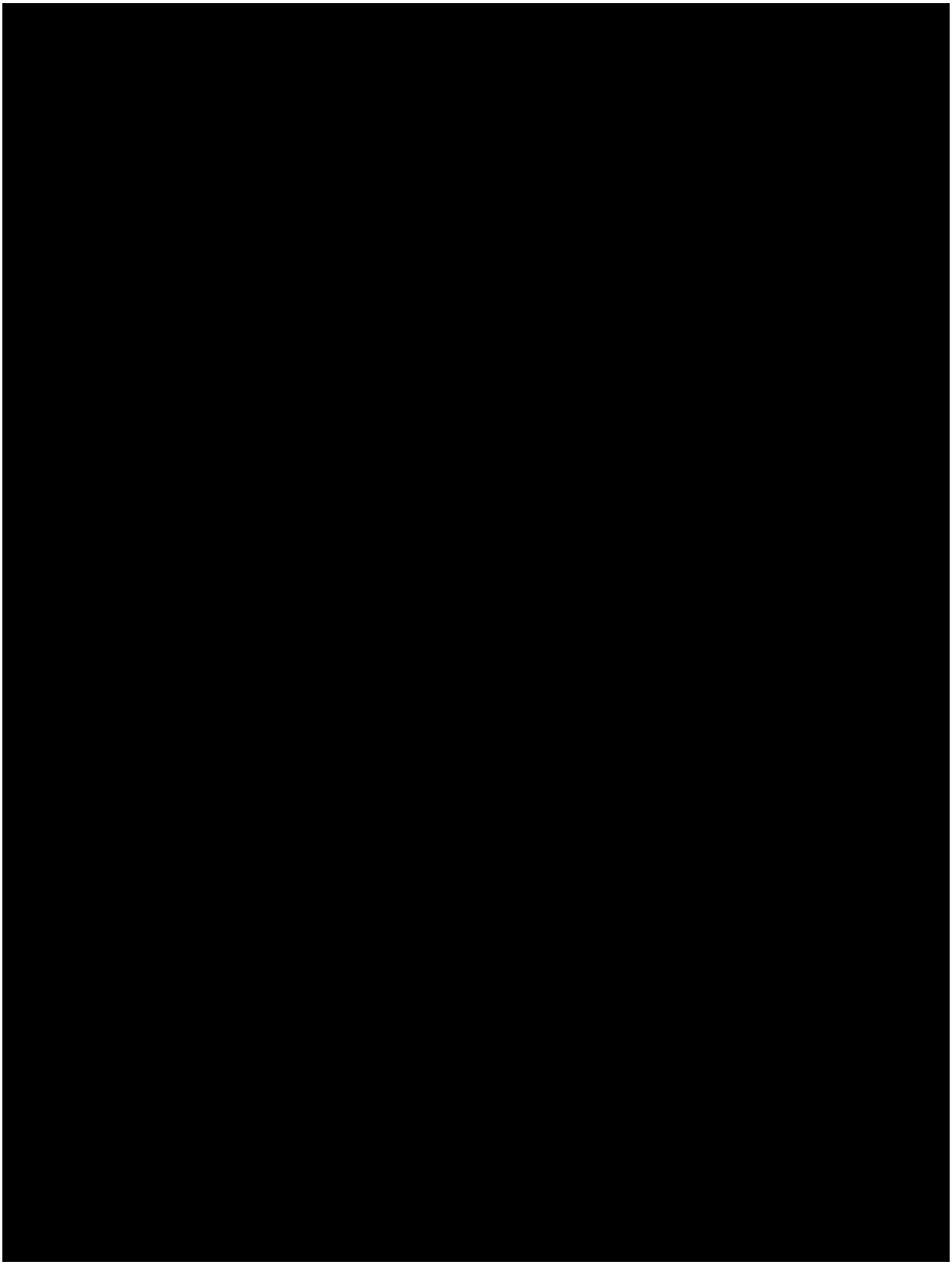
Subjects will be evaluated every 12 weeks from Baseline up to Week 36. Safety evaluations will be included in the regular visits; in addition, a safety follow-up visit will be performed 20 weeks after the last study visit (i.e. Week 36) and will take place at Week 56 for subjects completing the study according to the protocol. In addition, subjects in the T2T arm will be seen for safety monitoring at Visit 4 (Week 4) and Visit 5 (Week 8). Subjects who prematurely discontinue completely from the study for any reason should return for the final visit to conduct the Week 36 assessments (4 weeks after the last study treatment administration), then also return after an additional 20 weeks for a final follow-up visit, corresponding to Week 56 assessments.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
• To demonstrate that the efficacy of a T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach as measured by percentage of subjects achieving an ASAS40 response at Week 24.	• Percentage of subjects achieving an ASAS40 response at Week 24.
Secondary objectives	**Endpoints for secondary objectives**
• To demonstrate that the efficacy of the T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of subjects achieving an ASAS40 response at Week 12.	• Percentage of subjects achieving an ASAS40 response at Week 12.
• To demonstrate that the efficacy of the T2T (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of subjects achieving an Ankylosing SpondyloArthritis Disease Activity Score (ASDAS) clinically important improvement (defined as change from Baseline (BSL) of ≥ 1.1) at Week 12 and Week 24.	• Percentage of subjects achieving an ASDAS clinically important improvement (defined as change from BSL of ≥ 1.1) at Week 12 and Week 24.
To demonstrate that the efficacy of the T2T (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of patients achieving an ASDAS major improvement (defined as change from BSL of ≥ 2.0) at Week 12 and Week 24.	Percentage of patients achieving an ASDAS major improvement (defined as change from BSL of ≥ 2.0) at Week 12 and Week 24.
• To demonstrate that the efficacy of the T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of subjects achieving ASDAS < 1.3 at Week 12 and Week 24.	• Percentage of subjects achieving ASDAS < 1.3 at Week 12 and Week 24.
• To demonstrate that the efficacy of the T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of subjects achieving ASDAS < 2.1 (low disease activity) at Week 12 and Week 24.	• Percentage of subjects achieving ASDAS < 2.1 (low disease activity) at Week 12 and Week 24.

Objectives	Endpoints
• To demonstrate that the efficacy of the T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach based on the percentage of subjects achieving ASAS 20% response (ASAS20), ASAS partial remission (PR), and Bath Ankylosing Spondylitis Disease Activity Index 50% response (BASDAI50) responses at Week 12 and Week 24.	• Percentage of subjects achieving ASAS20, ASAS PR, BASDAI50 responses at Week 12 and Week 24.
• To demonstrate that the T2T approach (with secukinumab as first-line biologic) is superior to the SOC approach in terms of improvement of disease activity, function, axial mobility, and quality of life measures at Week 12 and Week 24 as compared to Baseline according to: o BASDAI o ASDAS o C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) o Bath Ankylosing Spondylitis Functional Index (BASFI) o Bath ankylosing spondylitis metrology index (BASMI) and chest expansion o Global assessment of disease activity (patient/physician) and general pain on Visual Analog Scale (VAS) o ASAS health index (ASAS-HI) o Short Form Health Survey (SF-36) o Ankylosing Spondylitis Quality of Life (ASQoL) o Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue).	• Improvement of disease activity, function, axial mobility, and quality of life measures at Week 12 and Week 24 as compared to Baseline according to: o BASDAI o ASDAS o CRP and ESR o BASFI o BASMI and chest expansion o Global assessment of disease activity (patient/physician) and general pain on the VAS o ASAS-HI o SF-36 o ASQoL o FACIT-Fatigue
• To demonstrate overall safety and tolerability of secukinumab.	• The number (and percentage) of patients with treatment-emergent adverse events (AEs).



2 Statistical methods

2.1 Data analysis general information

All categorical data will be presented in terms of frequencies and percentages. Summaries of continuous data will be presented in terms of mean, standard deviation (SD), median, lower and upper quartiles (for most variables), minimum and maximum, the number of missing data points (for most variables) and the number of non-missing data points.

For descriptive statistics, the following number of decimal places will be used: arithmetic mean, median, lower quartile and upper quartile to 1 more decimal places than the raw data; minimum and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data. Percentages will be presented to 1 decimal place.

2.1.1 General definitions

Study treatment: Study treatment refers to:

1. Investigational treatment Treat to Target (T2T) = secukinumab 150 mg and/or 300 mg and/or adalimumab biosimilar 40 mg (GP2017)
2. Standard of Care (SOC) treatment up to the maximum recommended dose at the discretion of the investigator

The **treatment phase** is defined as the period from randomization until end of the last treatment period with treatment periods defined as:

- Period 1: date of randomization until day before visit Week 12
- Period 2: date of visit Week 12 until day before visit Week 24

- Period 3: date of visit Week 24 until day before visit Week 36

The following exceptions are made to these definitions:
- If visit Week 12 or 24 is missing but the next visit is documented, the visit date is interpolated in the middle between the earlier and the later visit.
- End dates of period 1, 2, 3: If not further visit was performed during the treatment phase after start of the period, the end date is set to the documented end of treatment date or to the period start date, if no treatment was applied in this period.
- End date of period 3: If the documented end of treatment date is on visit Week 36 date or later, the end date of period 3 is set to the end of treatment date.
- Treat-to-Target group: If treatment was not applied at visit Week 12 or 24, or the last dose of the previous period was still applied on the date of visit, the start date of period 2 resp. 3 is set to the date of first dose in this period. Cases where the last dose of the previous period was still applied on the visit date are identified by the same dose as in the previous period applied on the visit date, but treatment was switched at the first dose after the visit.

Treat-to-Target regimen

Starting from Baseline, subject will be treated with secukinumab 150 mg subcutaneous (s.c.) weekly until Week 4 and then at Week 8.

At Week 12

- If the subject achieves and maintains an ASDAS clinically important improvement (i.e. change from Baseline in ASDAS $\geq$ 1.1 indicating subjects is a responder), then the subject will continue with secukinumab 150 mg s.c. every 4 weeks up to Week 32.
- If the subject did not achieve ASDAS clinically important improvement (i.e. non-responder) then the subject will receive an escalated dose of secukinumab 300 mg s.c. every 4 weeks until Week 20.

At Week 24

Subjects who are receiving secukinumab 300 mg and
- Achieves ASDAS clinically important improvement (i.e. responder) will continue with secukinumab 300 mg s.c. every 4 weeks up to Week 32.
- Do not achieve ASDAS clinically important improvement (i.e. non-responder), will be switched to adalimumab biosimilar (GP2017) 40 mg s.c. every 2 weeks until Week 34.

Escape arm
- Subjects who are receiving 150 mg secukinumab (i.e. were responders at Week 12) can be escalated at Week 24 to 300 mg secukinumab every 4 weeks until Week 32 if they experience a loss of response, where loss of response is defined as ASDAS change from Baseline <1.1.

If the ASDAS measurement is missing at a visit, it is assumed that the planned dose continues for the next treatment period.

Standard of Care Regimen

Patients will receive treatment according to local practice standards by their treating physician following the current treatment recommendations with NSAIDs as the first-choice drug treatment and disease-modifying anti-rheumatic drugs (DMARDs) for patients with active disease because of a lack of response, intolerance, or contraindication to NSAIDs (van der Heijde et al 2017). Patients will be seen every 12 weeks or more often, if clinically indicated up to Week 36; assessment of the outcome parameters will be performed at Week 12, Week 24 and Week 36.

Study treatment (T2T) start and end date: Study treatment start date is defined as the first date of study drug administration and recorded on the Drug Administration Record (DAR) Electronic Case Report Form (eCRF) page. Similarly, study drug end date is defined as the last date of study drug administration and is recorded on the DAR eCRF page.

SOC treatment start and end date: SOC treatment start date is defined as the first date of any SOC drug for AxSPA treatment after randomization. Similarly, SOC drug end date is inferred as the last date of any SOC drug administration for AxSPA treatment within the treatment phase.

Study day: Study Day 1 is defined as the first day of administration of randomized study treatment. Study day will be calculated as (event date – study drug start date + 1 day) for events that occurred on or after study drug start date (e.g. visit, lab samples, AEs). For events prior to study drug start date (e.g. time since diagnosis), study day will be negative and calculated as (event date – study drug start date).

Baseline and post-Baseline: Baseline value refers to the value of the last non-missing measurement collected prior to administration of the first dose of study treatment (screening or Baseline visit). A post-Baseline value refers to a measurement taken after the first dose of study treatment.

Change from Baseline: The difference of measure between post-Baseline and Baseline is called change from Baseline.

Percent change from Baseline: The percent change from Baseline will be calculated as below:

((post-Baseline value – Baseline value) /Baseline value)*100.

On-treatment period: The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment or end of treatment phase, whichever is later.

2.1.2 Visit windows for data analysis

Visit windows will be used for data analyses which are summarized by visit. This is based on scheduled visits and comprises a set of days around the nominal visit day. Randomization of subjects will take place at Baseline; subjects will have a maximum of 14 scheduled post-Baseline assessments and 1 follow-up assessment after 20 weeks. The data will be analyzed at Baseline, Week 12, Week 24 and Week 36. A follow-up visit will take place at Week 56.

In case of more than one post-Baseline assessment due to unscheduled visits, the assessment closest to the scheduled post-Baseline day will be used for analysis. For the summary of notable

laboratory abnormalities, the most extreme post-Baseline measurement will be used for analysis in case of more than one post-Baseline assessment. In the event two measurements are taken equally apart (e.g., 1 day before target date and 1 day after), the earlier one will be used.

Table 2-1 Assessment windows for scheduled visits

Analysis Visit	Week	Scheduled Day	Visit Window
Baseline	BSL	1	-28 days to Day 1*
Week 12	12	85	Day 2-Day 127
Week 24	24	169	Day 128-Day 211
Week 36	36	253	Day 212-Day 364

* Baseline measurement before the first drug administration.

2.2 Analysis sets

Enrolled Set (ENR): The ENR will comprise all patients, who provided inform consent.

Randomized Analysis Set (RAS): The RAS is defined as all subjects who were randomized. Unless otherwise specified, misrandomized subjects will be excluded from the RAS. Misrandomized patients are defined as cases where subjects were mistakenly randomized by the investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind treatment was not administered to the subject.

Full Analysis Set (FAS): The FAS comprises all subjects to whom study treatment/reference treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set: The Safety Set includes all subjects who received at least one dose of study treatment/reference treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the first dose of study/reference treatment.

2.2.1 Subgroup of interest

Interactions between treatment and selected Baseline demographics and disease characteristics will be explored for ASAS 40 response at Week 24. Subgroup analyses for the primary efficacy endpoint will be performed on the following based on the patient's Baseline status:

- Gender: (Male, Female).
- Age group (year): (≥ 18 to ≤ 64, > 64 to ≤ 75, > 75).
- Disease severity based on ASDAS at Baseline: (< 1.3, ≥ 1.3 to < 2.1, ≥ 2.1).
- CRP blood level at Baseline (mg/l): (≤ 5, > 5).

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The FAS and ENR will be used to prepare a summary of patient disposition. TheFAS will be used to prepare a patient disposition listing.

The number and percentage of subjects who completed the study and discontinued from the study will be summarized by treatment with reasons for premature discontinuation. In addition, the number of screen failures with reasons will be presented for all screened subjects. Patient identification number and whether subjects completed or discontinued from the study will be listed, with date of last dose and primary reason for premature discontinuation.

2.3.2 Protocol deviation

The number and percentage of subjects with protocol deviations will be tabulated by category and deviation for the FAS. Separate summary for protocol deviation due to COVID - 19 will be provided for FAS. Subjects with protocol deviations will be listed with date and study day of occurrence, deviation and severity codes.

The number of subjects included in each analysis set will be tabulated for FAS Reasons for exclusion from analysis sets will be tabulated for the FAS. Patient exclusion from analysis sets will be listed for all subjects with reasons for exclusion (i.e., both protocol and non-protocol deviations).

2.3.3 Demographic characteristics

Demographic and Baseline characteristics will be listed and summarized descriptively by treatment group and total for the FAS and the safety set.

The following demographic and vital signs variables collected in the eCRF at Baseline will be summarized:

- Sex (Male, Female)
- Age (in years)
- Age category ($\geq$ 18 - $\leq$ 64, > 64 - $\leq$ 75, > 75)
- Country (Germany, Other)
- Race (Caucasian, Black, Asian, Other)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- BMI (< 25 kg/m^2, 25 - < 30 kg/m^2 and $\geq$ 30.0 kg/m^2)
- Vital signs (sitting systolic/diastolic blood pressure (mmHg), sitting pulse rate (bpm))
- Smoking status (never, current, former)

The following Baseline disease characteristics will be summarized:

- Diagnosis of axSpA (Yes, No)
- Classification of axSpA (r-axSpA, nr-axSpA)
- Time since first signs and symptoms of axSpA (years)
- Inflammatory back pain: (Yes, No)
- Time since onset of inflammatory back pain until ax-SpA diagnosis (years)
- Arthritis: (Yes, No)
- Uveitis: (Yes, No)
- Dactylitis: (Yes, No)
- Enthesitis (Yes, No)
- Psoriasis: (Yes, No)
- Crohn's disease or colitis: (Yes, No)
- [redacted]
- Good response to NSAIDs: (Yes, No)
- Family history for SpA: (Yes, No)
- HLA-B27 positive: (Yes, No)
- Elevated CRP: (Yes, No)
- [redacted]
- Radiographic evidence for sacroiliitis according to the mNY criteria : (Yes, No)
- ASDAS-CRP
- ASDAS- ESR
- ESR
- CRP
- C-Reactive Protein (mg/L) (≤ 5, > 5)
- Quick CRP
- Quick C-Reactive Protein(mg/L) (≤ 5,> 5)
- [redacted]
- [redacted]
- [redacted]
- Back pain (BASDAI)
- Overall Level Fatigue/Tiredness (BASDAI question 1)

- Overall Neck, Back, Hip Pain (BASDAI question 2)
- Pain Joint O/T Neck, Back, Hip (BASDAI question 3)
- Discomfort Tender Area to Touch (BASDAI question 4)
- Overall Level Morning Stiffness (BASDAI question 5)
- Morning Stiffness From Wakeup (BASDAI question 6)
- Patient/physician global assessment
- ASAS-HI
- BASFI
- BASMI
- Chest expansion
- SF- 36
- FACIT- fatigue

Time since (in years) of symptoms is calculated as (start date of treatment – date of first diagnosis of symptom + 1)/365.25.

2.3.4 Relevant medical history/ current medical condition

Medical history/ current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. History/conditions will be summarized for the FAS by primary system organ class, preferred term (PT), treatment group and overall. Verbatim recorded history/conditions will be listed together with the coded terms, date of diagnosis/surgery and whether the problem was ongoing at start of the study.

2.3.4.1 Cardiovascular risk factors

Number and percentage of subjects with specific cardiovascular risk factors will be summarized. In addition, the number and percentage of subjects with 0, 1, 2, 3, 4 or more cardiovascular risk factors will be summarized. Cardiovascular risk factors are defined as the following medical histories/conditions:

- CCV history/condition
- Hypertension
- Lipidemia (dyslipidemia/hyperlipidemia)
- Diabetes (complicated/uncomplicated)
- Prior transient ischemic attack
- Prior hemorrhagic stroke
- Prior ischemic stroke
- Prior stroke (unknown type)
- Myocardial infraction
- Atrial fibrillation

- Supraventricular
- Tachycardia
- Deep vein thrombosis
- Pulmonary embolism

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

2.4.1 Study treatment

Duration of exposure

The number of injections will be summarized by treatment groups, overall and within treatment periods . Duration of exposure to the study treatment will be calculated as the number of days between the first dose date and the last dose date exposed to that treatment over the specified period (expressed as: Duration of exposure = Date of last known dose of study drug – Date of first dose of study drug + 1).

The duration of exposure (in days) to the study treatment by treatment group (T2T, SOC, Other and Overall) will be summarized for the safety set as below

- a continuous variable with the standard descriptive statistics, and
- a categorical variable classified into < 12 weeks, ≥ 12 and < 24 weeks, ≥ 24 and < 36 weeks, ≥ 36 weeks with number and percentage of subjects in each category.
- On-treatment exposure = Date of last known dose of study drug – Date of first dose of study drug + 1 + 30).

Furthermore, the T2T arm will be summarized by treatment (secukinumab 150 mg, secukinumab 300 mg, adalimumab 40 mg). The T2T arm will also be summarized for actual treatment arm.

Similarly, in the SOC arm all medications will be summarized along with their drug class.

2.4.2 Prior, concomitant and non-drug therapies/procedures

Each medication has the start and end dates recorded on the eCRF. Prior medications are defined as those medications which were taken and stopped prior to first dose of study treatment. Concomitant medications are defined as any medication given at least once between the day of first dose of randomized study treatment and the last day of study visit, including those which were started pre-Baseline and continued into the treatment period. The below summary tables will be reported for:

a. Prior medication
b. Concomitant medications which started prior or on/after the first dose of study treatment but before end of the treatment phase.
c. Follow-up medications which started after the treatment phase

Rescue medications will be summarized separately by treatment group.

All prior and concomitant medications will be coded using the latest version of the WHO drug dictionary. All concomitant medications will be listed and summarized in alphabetical order according to the Anatomical Therapeutic Chemical (ATC) classification system and PT by treatment group. Tables will also show the overall number and percentage of subjects receiving at least one treatment of a particular ATC. Non drug therapies and procedures will be listed according to collected term in alphabetical order.

Categories of concomitant medications are outlined in Appendix 5.3.

For handling of missing or incomplete start and end dates, see Appendix 5.1.3 of this document.

All summaries will be on the safety set.

2.5 Analysis of the primary objective

The primary objective of the study is to demonstrate an advantage of an intensified T2T (secukinumab) approach, as measured by the proportion of subjects achieving ASAS40 response, when compared to a SOC treatment regimen in subjects with active axSpA inadequately responding to NSAID therapy.

2.5.1 Primary endpoint

The primary endpoint variable is the proportion of subjects achieving treatment response as defined by the ASAS40 criteria at Week 24.

ASAS responder: ASAS responder will be derived based on the following 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 a VAS scale.

Additional assessment domains:

5. Spinal mobility represented by the BASMI lateral spinal flexion assessment.
6. CRP (acute phase reactant).

ASAS response criteria 40% (ASAS 40): ASAS40 response is defined as an improvement of ≥ 40% and ≥ 2 units on a scale of 10 in at least 3 of the 4 domains and no worsening at all in the remaining domain.

ASAS response criteria 20% (ASAS 20): ASAS20 response is defined as an improvement of ≥ 20% and ≥ 1 unit on a scale of 0 to 10 in at least 3 of the 4 domains, and no worsening of >=20% and >=1 unit at all in the remaining domain.

ASAS partial remission (PR): ASAS partial response is defined as a score of < 2 units on a scale of 10 for all 4 core ASAS domains.

2.5.2 Statistical hypothesis, model, and method of analysis

The null hypothesis to be rejected is that the odds of ASAS40 response at Week 24 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 24 are higher under the secukinumab T2T approach compared to a SOC regimen.

Let p_j denote the proportion of ASAS40 responders at 24 weeks for treatment group j, j=0,1 where

0 corresponds to the SOC regimen

1 corresponds to the secukinumab T2T regimen

The following hypotheses will be tested:

H_0: $(p_1 / 1\text{-}p_1)) / (p_0 / 1\text{-}p_0)) = 1$ vs. H_A: $(p_1 / 1\text{-}p_1)) / (p_0 / 1\text{-}p_0)) \neq 1$

In other words:

H_A: The odds ratio (OR) of achieving an ASAS40 response at Week 24 for the comparison of secukinumab T2T vs. SOC is different from 1.

The **primary analysis** will be performed comparing treatments with respect to the primary efficacy variable in a multiple logistic regression model with treatment and center as factors and weight as well as Baseline CRP level as covariates. The adjusted OR, the corresponding 95% confidence interval (CI) and the p-value will be given. The H_0 of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is < 0.05; however, superiority of secukinumab T2T approach will be claimed only if the direction is correct, i.e. if the odds of response are larger under secukinumab T2T approach.

Tables will also show the number and percentage of patients achieving ASAS40 response.

The primary efficacy analysis will be based on the FAS. The primary analysis will be performed when all subjects have completed the Week 24 assessment.

2.5.3 Handling of missing values/censoring/discontinuations

Subjects will be analyzed irrespective of adherence to assigned treatment regimen. Subjects without a valid ASAS40 assessment at Week 24 will be regarded as non-responders for the primary analysis.

In case of substantial missing data in the primary analysis, alternative approaches will be assessed by repeating the logistic regression model using ways to handle missing values. These may include, but are not limited to:

- Multiple imputation
- Observed data analysis

2.5.4 Supportive analyses

Supportive analyses will be conducted in order to provide evidence that the results seen from the primary model are robust. Possible effect modification due to patient characteristics will be explored by subgroup analyses for sex (male, female), age class (≥ 18 to ≤ 64, > 64 to ≤ 75, > 75) (years), disease severity based on ASDAS (< 1.3, ≥ 1.3 to < 2.1, ≥ 2.1) and CRP blood level

(≤ 5, > 5) (mg/L) at Baseline. The primary model may also be recalculated with these factors included as well as with the respective terms for a subgroup by treatment interaction.

2.6 Analysis of the key secondary objective

There are no key secondary objectives in this study.

2.7 Analysis of secondary [redacted] efficacy objective(s)

2.7.1 Secondary [redacted] endpoints

Secondary efficacy [redacted] assessments will be evaluated based on the FAS and listed by treatment and visit on the FAS.

The following secondary efficacy [redacted] endpoints will be evaluated applying methods as defined below:

Table 2-2 Secondary [redacted] variables

Secondary [redacted] endpoint	Time point	Model/Method
ASAS40 response	Week 12 [redacted]	Multiple logistic regression
ASAS20 response	Week 12, Week 24 [redacted]	Multiple logistic regression
ASAS PR	Week 12, Week 24 [redacted]	Multiple logistic regression
AS disease activity score • ASDAS clinically important improvement (defined as change from BSL of ≥1.1) • ASDAS major improvement (defined as change from BSL ≥ 2.0)	Week 12, Week 24 [redacted]	Multiple logistic regression
• ASDAS<1.3	Week 12, Week 24 [redacted]	Multiple logistic regression
• ASDAS<2.1 (low disease activity)	Week 12, Week 24 [redacted]	Multiple logistic regression
BASDAI 50	Week 12, Week 24 [redacted]	Multiple logistic regression
[redacted]		

Secondary [redacted] endpoint	**Time point**	**Model/Method**
Improvement of disease activity, function, axial mobility, and quality of life measures compared to Baseline according to:		
BASDAI change from Baseline	Week 12, Week 24 [redacted]	MMRM
ASDAS change from Baseline	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in CRP and ESR	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in BASFI	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in BASMI	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in chest expansion	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in Patient's Global assessment of disease activity	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in Physician's Global assessment (VAS scale) of disease activity	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in ASAS- HI	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in SF-36 domain scores	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in SF-36 PCS and MCS	Week 12, Week 24 [redacted]	MMRM
SF-36 Response	Week 12, Week 24 [redacted]	Multiple logistic regression
Change from Baseline in ASQoL	Week 12, Week 24 [redacted]	MMRM
Change from Baseline in FACIT-Fatigue	Week 12, Week 24 [redacted]	MMRM

[redacted]

Secondary endpoint [redacted]	Time point	Model/Method
[redacted]		

2.7.1.1 ASAS40 response

Response at Week 12 [redacted] to ASAS40 will be analyzed analogously to the primary endpoint (see Section 2.5.1 for definition of the ASAS40 responder).

2.7.1.2 ASAS20 response

Response at Week 12, Week 24 [redacted] to ASAS20 will be will be analyzed analogous to the primary endpoint (see Section 2.5.1 for definition of the ASAS20 responder).

2.7.1.3 ASAS partial remission

The proportion of patients meeting the ASAS definition for PR at Week 12, Week 24 [redacted] will be analyzed by means of a multiple logistic regression model including treatment and center as factors and weight as covariate (see Section 2.5.1 for definition of the ASAS PR responder).

2.7.1.4 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 (called enthesitis, or inflammation of tendons and ligaments)
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. BASDAI is a quick and simple index taking between 30 seconds and 2 minutes to complete. At least 4 questions should be non-missing to calculate the BASDAI score (Haywood et al 2002). Otherwise, BASDAI score will be missing. If Q5 and/or Q6 are missing or one of Q1 to Q4 is missing 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 the sum should be divided by 3.

The BASDAI will be summarized descriptively (total score, change from Baseline) by treatment group and overall, at Week 12, Week 24 [redacted] for FAS. The between-treatment difference in change from Baseline in BASDAI will be also evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline BASDAI score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline BASDAI score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

2.7.1.5 Bath ankylosing spondylitis disease activity index 50% response (BASDAI50)

The subjects who achieve ≥50% BASDAI score at post-Baseline from Baseline will be considered as BASDAI50 responders.

The proportion of subjects achieving the BASDAI50 response criteria at Week 12, Week 24 [redacted] will be analyzed by multiple logistic regression model with treatment and center as factors and weight and Baseline BASDAI as covariates.

2.7.1.6 AS disease activity score

The ASDAS-CRP (based on Quick-CRP) and ASDAS-ESR (Ankylosing Spondylitis Disease Activity Score) will be utilized to assess the disease activity status. Parameters used for the ASDAS include: total back pain (BASDAI question 2), the patient global assessment of disease activity (ASAS component 1), peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/liter (or ESR) (Sieper et al 2009, Lukas et al 2009).

The ASDAS formulas are as follows:

ASDAS-CRP/ ASDAS-quick CRP = 0.121 x total back pain + 0.110 x patient global + 0.073 x peripheral pain/swelling + 0.058 x duration of morning stiffness + 0.579 x ln(CRP +1).

ASDAS-ESR = 0.113 x patient global + 0.293 x √ESR + 0.086 x peripheral pain/swelling + 0.069 x duration of morning stiffness + 0.079 x total back pain.

CRP is in mg/liter, ESR is in mm/h; the range of other variables is from 0 to 10; ln represents the natural logarithm; √ represents the square root. If any of the ASDAS components are missing ASDAS will not be calculated.

ASDAS (CRP) will be assessed by the investigator via eCRF at screening and Baseline for all patients in order to estimate the eligibility of the patient. Only patients with ASDAS > 2.1 will be enrolled. In addition, the ASDAS will be calculated via eCRF at Week 12 and Week 24 in order to estimate the response and to decide further treatment. Locally assessed quick CRP values will be used in order to evaluate disease activity for these purposes.

Disease activity states are inactive disease, low disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states were < 1.3 between inactive disease and low disease activity, < 2.1 between low disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cutoffs for

improvement scores were a change of ≥ 1.1 unit for "minimal clinically important improvement" and a change of ≥ 2.0 units for "major improvement" (Machado et al 2011, Machado et al 2018).

The number and percentage of patients in each of the categories will be presented for Baseline visit, Weeks 12, 24 and 36. The proportion of subjects meeting the ASDAS definition of inactive disease (< 1.3), ASDAS clinically important improvement (change from Baseline by ≥ 1.1), ASDAS major improvement (change from Baseline by ≥2) and ASDAS low disease activity (< 2.1) at Week 12, Week 24 [redacted] will be evaluated using a multiple logistic regression model with treatment group and center as factors and weight and Baseline ASDAS as covariates.

Furthermore, the ASDAS-CRP will be summarized descriptively (total score, change from Baseline) by treatment group and overall, at Week 12, Week 24 [redacted] for FAS. The between-treatment difference in change from Baseline in ASDAS will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline ASDAS index score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline ASDAS index score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

2.7.1.7 Bath ankylosing spondylitis functional index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those patients with AS. The 10 questions were chosen with major input from patients with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patient's ability to cope with everyday life. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the 10 scales gives the BASFI score – a value between 0 and 10. If there are missing questions the average of the non-missing items is used (Braun et al 2009, van Tubergen et al 2001).

1. Put socks or tights without help or aids (0-10).
2. Bend to pick up pen without an aid (0-10).
3. Reaching high shelf without help or aids (0-10).
4. Up from armless chair without help (0-10).
5. Getting off from floor lying your back (0-10).
6. Standing 10 minutes without discomfort (0-10).
7. Steps without handrail or walking aid (0-10).
8. Looking shoulder without turning body (0-10).
9. Doing physically demanding activities (0-10).
10. Full day activities at home or work (0-10).

The BASFI will be summarized descriptively (total score, change from Baseline) by treatment group and overall, at Week 12, Week 24 [redacted] for FAS. The between-treatment difference in change from Baseline in BASFI will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline BASFI score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline BASFI score by analysis visit will be included as interaction terms in the model. An unstructured

covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

2.7.1.8 Bath ankylosing spondylitis metrology index and chest expansion (BASMI)

The BASMI is a validated instrument that uses the minimum number of clinically appropriate measurements that assess accurately axial status, with the goal to define clinically significant changes in spinal movement. Parameters include:

1. Lateral spinal flexion (cm)
2. Tragus-to-wall distance (cm)
3. Lumbar flexion (modified Schober) (cm)
4. Maximal intermalleolar distance (cm)
5. Cervical rotation angle (°)

Additionally, the following assessments should be taken:

6. Chest expansion
7. Occiput-to-wall distance

The individual conversion of BASMI categories is as below.

1. Lateral lumbar flexion (cm)

Side		Standing	Bending	Difference	Larger difference	Mean of larger difference
Right	Reading 1	xx	xx	xx	xx*	xx**
	Reading 2	xx	xx	xx		
Left	Reading 1	xx	xx	xx	xx*	
	Reading 2	xx	xx	xx		

Find the difference of standing and bending position for all readings, take largest difference from each side and use average of larger difference of both sides.

2. Tragus-to-wall distance* (cm)

	Right (1)	Left (2)	Average of (1) and (2)	Shortest average
Reading 1	xx	xx	xx	xx**
Reading 2	xx	xx	xx	

Find the average of both sides (right and left) for all readings and use shortest average.

3. Modified Schober Index (Lumbar flexion*) (cm)			
	Bending	Difference (minus 15 cm standing distance)	Higher difference
Reading 1	xx	xx-15	xx**
Reading 2	xx	xx-15	
Subtract 15 from all readings and use higher difference.			

4. Intermalleolar distance (cm)		
Reading 1	Reading 2	Higher of Reading 1 and Reading 2
xx	xx	xx**
Use higher value from all readings.		

5. Cervical rotation angle*(°)				
Side	Reading 1	Reading 2	Higher of Reading 1 and Reading 2	Mean of higher reading
Right	xx	xx	xx*	xx**
Left	xx	xx	xx*	
Find the higher reading from both sides and use mean of higher reading.				

6. Chest expension				
	Inspiration	Expiration	Difference	Higher diffrence
Reading 1	xx	xx	xx*	xx**
Reading 2	xx	xx	xx*	
Find the higher reading from both sides and use higher difference.				

After finalizing individual BASMI score (**) use below method to convert each BASMI score to a 0 to 10 scale.

The assessment A of the first five components is transformed into the scores S using the equations given in table below (van der Heijde et al 2006). The average score of the five assessments S gives the BASMI linear result. All 5 components must be available to calculate the score.

Table 2-3 Equations for the conversion of the assessments A into scores S for the 5 components of the BASMI linear

	S=0	Between 0 and 10	S=10
Lateral lumbar flexion* (cm)	A ≥ 21.1	S = (21.1 – A)/2.1	A ≤ 0.1
Tragus-to-wall distance* (cm)	A ≤ 8	S = (A – 8)/3	A ≥ 38
Lumbar flexion (modified Schober) (cm)	A ≥ 7.4	S = (7.4 – A)/0.7	A ≤ 0.4
Intermalleolar distance (cm)	A ≥ 124.5	S = (124.5 – A)/10	A ≤ 24.5
Cervical rotation angle*(°)	A ≥ 89.3	S = (89.3 – A)/8.5	A ≤ 4.3

* For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken.
If a score lies beyond the range 0-10, the values 0 or 10 have to be used, respectively.
The BASMI linear is the mean of the five scores.

The BASMI linear will be summarized descriptively (total score change, from Baseline) by treatment group and overall, at Week 12, Week 24 [redacted] for FAS. The between-treatment difference in change from Baseline in BASMI linear will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline BASMI score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline BASMI score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

The two additional assessments (chest expansion and occiput-to-wall distance) will be shown in the listing for BASMI for each treatment group.

2.7.1.9 Change in patient's/physician's global assessment of disease activity

The patient's/physician's global assessment score (VAS scale) will be collected in eCRF at scheduled visits. The patient's global assessment of disease activity will be performed using a 100 mm VAS ranging from not severe to very severe, after the question "How active was your disease on average during the last week?". The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today.".

The patient's/physician's global assessment score will be summarized descriptively (total score change from Baseline) by treatment group and overall, at Week 12, Week 24 [redacted] for FAS.

The between-treatment difference in change from Baseline in patient's global disease assessment will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline patient's global disease assessment VAS score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline patient's global disease assessment VAS score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the

secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

Same methodology will be repeated for physician's global assessment of disease activity with associated changes for Baseline values.

[redacted]

2.7.1.12 ASAS health index

The ASAS-HI is a disease-specific questionnaire that was developed based on the comprehensive International Classification of Functioning, Disability and Health Core Set (also known as the ICF Core Set) for AS (Kiltz et al 2014). The ASAS HI is a linear composite measure and contains 17 items (dichotomous response option: "I agree" and "I do not agree"), which cover most of the international classification of functioning (ICF) Core Set. The ASAS HI contains items addressing categories of pain, emotional functions, sleep, sexual function, mobility, self-care, and community life. The total sum of the ASAS HI ranges from 0 to 17, with a lower score indicating a better health status.

A total score can be analyzed if no more than 20% of the data (i.e. 3 items) are missing. The total score is calculated as follows for respondents with one to a maximum of three missing responses: Total score = (x / 17-m)*17, where x=item summation score and m number of missing items. Cases with more than three missing responses cannot be allocated a total score.

In addition, the Environmental Factor (EF) Item Set contains items addressing categories of support/relationships, attitudes and health services. The EF Item Set contains 9 dichotomous items with an identical response option but without a sum score because of its multidimensional nature (Kiltz et al 2014).

The ASAS-HI will be summarized descriptively (total score, change from Baseline) by treatment group and overall at Week 12, Week 24 [redacted] for FAS. The between-treatment difference in change from Baseline in ASAS-HI will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline ASAS-HI score and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline ASAS-HI score by analysis visit will be included as interaction terms in the model. An unstructured

covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

2.7.1.13 Short form-36 version 2 (acute form)

The following variables will be evaluated:

- SF-36 domain scores
- SF-36 PCS and MCS
- SF-36 responder analyses

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 (Ware and Sherbourne 1992). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware and Sherbourne 1992). 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 8 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.

The SF-36 summary scores, PCS and MCS will be summarized descriptively (total score, change from Baseline) by treatment group and overall at Week 12, Week 24 [redacted] for FAS. For the change in SF-36 summary scores, PCS and MCS between-treatment differences will be evaluated utilizing a MMRM for full analysis set. Treatment group and analysis visit will be included as categorical factors in the model and Baseline SF-36 score (PCS or MCS) and weight as continuous covariates. Treatment group by analysis visit and Baseline SF-36 score (PCS or MCS respectively) by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

For the responder analyses the proportion of patients achieving a clinically meaningful difference in SF-36 summary score, PCS(=3.4) and MCS(=4.6) at Week 24 will be analyzed by means of a multiple logistic regression model with treatment and center as factors and weight and Baseline score value as continuous covariates.

2.7.1.14 Ankylosing spondylitis quality of life

The ASQoL is a self-administered questionnaire designed to assess health-related quality of life in adult patients with AS. 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 scores indicate 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 questionnaire requires approximately 6 minutes to complete. The purpose of the ASQoL is to assess the disease specific QoL of patients in this study.

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

The ASQoL will be summarized descriptively (total score, change from Baseline) by treatment group and overall at Week 12, Week 24 [redacted] for FAS. Between-treatment differences in the change from Baseline in the ASQoL will be evaluated using a MMRM with treatment group and analysis visit as factors as well as Baseline ASQoL score and weight as continuous covariates. Treatment group by analysis visit and Baseline ASQoL by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

2.7.1.15 Functional assessment of chronic illness therapy – fatigue

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue©) is a 13-item questionnaire (Cella et al 1993, Yellen et al 1997) that assesses self-reported fatigue and its impact upon daily activities and function. The purpose of FACIT-Fatigue in this study is to assess the impact of fatigue on patients with AS.

Subjects respond to each item on a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much) based on their experience of fatigue during the past 2 weeks. The scale score is computed by summing the item scores, after reversing those items that are worded in the negative direction (i.e. original response of 0 gets mapped to 4, 1=3, 2=2, 3=1, and 4=0). Numbering the questions from 1 to 13, it is evident that questions 7 and 8 are worded in the positive direction (4 indicates a desirable response) and all other questions are worded in the negative directions (4 indicates an undesirable response). Thus, it is necessary to reverse the responses for all questions except 7 and 8 for scoring purposes. When there are missing item scores, the scale score was computed by summing the non-missing item scores, multiplying by 13 (the total number of items in the scale) and dividing by the number of non-missing items (i.e. normalizing the results). The latter rule applied only when at least half of the items (seven or more) are non-missing. FACIT Fatigue scale score range from 0 to 52, where higher scores represent less fatigue (Cella et al 1993).

The FACIT-Fatigue will be summarized descriptively (total score change from Baseline) by treatment group and overall at Week 12, Week 24 [redacted] for FAS. Between-treatment differences in the change from Baseline in the FACIT-Fatigue total score will be evaluated using a MMRM with treatment group and analysis visit as factors as well as Baseline FACIT-Fatigue score and weight as continuous covariates. Treatment group by analysis visit and Baseline FACIT-Fatigue score by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups.

[redacted]

2.7.2 Statistical hypothesis, model, and method of analysis

Between-treatment comparisons for binary variables in the FAS population (e.g. ASAS20, ASAS40) at individual analysis visits will be evaluated using a logistic regression model with treatment and center as factors and weight as covariates. Odds ratios and 95% CI will be presented for appropriate treatment comparisons. Continuous variables will be evaluated, using a MMRM, with treatment group and analysis visit as factors and Baseline score for related assessment and weight as continuous covariates. Treatment group by analysis visit and Baseline related assessment by analysis visit will be included as interaction terms in the model. An unstructured covariance matrix will be assumed. If covariance matrix will not converge then other covariance structure will be used like compound symmetry, autoregressive structure etc. The treatment effect for the secukinumab T2T regimen at different analysis visits will be determined from the pairwise comparison performed between the 2 treatment groups. The adjusted least square means, point estimate of difference between treatment means, 95% CI for treatment difference and p-value will be presented.

2.7.3 Handling of missing values/censoring/discontinuations

Non-responder imputation will be applied to all secondary response variables. In case of substantial missing data in the secondary analysis, alternative approaches will be assessed by repeating the logistic regression model using ways to handle missing values. These may include, but are not limited to:

- Multiple imputation
- Observed data analysis

2.8 Safety analyses

Safety measurements include duration of exposure, vital signs, laboratory data and adverse events. All safety endpoints will be summarized using the Safety Set. Patients will be analyzed according to treatment received. No imputation will be carried out for missing data.

2.8.1 Adverse events (AEs)

All information obtained on AEs will be displayed by treatment group and subject. Summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (see Section 2.1.1) for definition of on-treatment period).

The count of treatment-emergent AEs, number (and percentage) of subjects with treatment-emergent AEs (defined as events started after the first dose of study treatment or events present prior to start of study treatment but increased in severity based on PT) will be summarized in the following ways:

- By treatment, primary system organ class and PT.
- By treatment, primary system organ class, PT and maximum severity.

Adverse events in the T2T arm will be summarized by 3 groups (secukinumab 150 mg, secukinumab 300 mg and adalimumab 40 mg).

Adverse events occurring in the SOC arm for patients treated with any of the following: secukinumab 150 mg, secukinumab 300 mg , adalimumab 40 mg and other will also be summarized under a separate SOC page.

Separate summaries will be provided for study treatment related AEs, death, SAEs, other significant AEs action taken leading to study drug withdrawn and AEs leading to dose adjustment (dose increase, dose reduce).

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (PT). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same PT, the AE with the greatest severity will be presented. System organ classes will be presented in alphabetical order, preferred terms will be sorted within system organ class in descending frequency of AEs in the T2T treatment group. If a subjects reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

For the legal requirements of ClinicalTrials.gov and EudraCT, 2 required tables on treatment emergent AEs which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class and PT on the safety set population.

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

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

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

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

In addition, all the treatment emergent AEs will be listed.

The by-subjects listing will include, SOC/PT/Verbatim term, start date, end date, severity, relationship to study drug, whether or not it is a serious AE, action taken with study drug and outcome. Duration will be calculated as (end date – start date + 1) and for ongoing AE (last visit date – start date + 1).

A summary of action taken with number and percentage of subjects will presented with dose increased, no dose change, dose reduced, drug interrupted, drug withdrawn, not applicable and unknown.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

A separate summary of deaths including on-treatment and post-treatment deaths will be provided.

All deaths in the clinical database will be listed with the investigator-reported principal cause. Deaths occurring after the first dose of study treatment until 30 days after the date of last treatment will be summarized. In addition, deaths occurring after the first dose of study treatment and before the date of last treatment will be summarized.

2.8.3 Laboratory data

All laboratory data will be listed with abnormal values flagged.

Laboratory data measured more than 30 days after the last dose of study drug is regarded as post-treatment and will not be summarized or analyzed, only listed.

The below laboratory parameter data will be analyzed.

Hematology: Hemoglobin, hematocrit, platelet count, red blood cell, WBC and differential WBC counts.

Clinical chemistry: glucose, urea, creatinine, total bilirubin, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

Lipid panel: High density lipoprotein, low density lipoprotein, cholesterol and triglycerides must be measured from a fasting blood sample.

Urinalysis: Protein, glucose, blood and WBCs.

For all continuous laboratory parameters, summary statistics for absolute and change from Baseline values will be provided at each visit. All laboratory data (including any unscheduled assessments) will be listed with abnormal values flagged.

For categorical urinalysis laboratory parameters (Glucose, Occult Blood, Protein), a frequency table of results will be produced by laboratory parameter, scheduled visit and treatment.

Shift tables for laboratory parameters will be provided in order to compare a subject's Baseline value to the value at each study visit, relative to the normal reference range for each lab parameter. Abnormal values marked in Section 5.4 will be used to evaluate whether a particular laboratory test value for each visit is normal, low or high relative to the Baseline value also categorized as normal, low or high. These summaries will be presented by laboratory parameter, visit and treatment group.

In addition, shift tables relative to the normal reference ranges will be used to summarize the change from Baseline to the most extreme post-Baseline for each laboratory parameter. For each laboratory test, the subjects will be classified into one of the four mutually exclusive groups (low, normal, high, and low + high), defined as follows:

- Low: at least one post-Baseline value below the normal range and none above the normal range
- High: at least one post-Baseline value above the normal range and none below the normal range
- Normal: all the post-Baseline values within the normal range
- Low + High: at least one post-Baseline value below the normal range and at least one above the normal range

Categorical parameters in the urinalysis panel will also be summarized with shift tables showing the shift from one categorical result to another.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable

2.8.4.2 Vital signs

Vital signs will include blood pressure and pulse rate measurements.

All vital signs data will be listed by treatment group, patient, and visit, and if ranges are available, abnormalities will be flagged. Abnormal values are marked in Section 5.4. All data, including data from unscheduled visits, will be considered when identifying abnormal values. Analysis of the vital sign measurements using summary statistics for the change from Baseline for each post-Baseline visit, minimum post-Baseline value and maximum post-Baseline value will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from Baseline will only be summarized for subjects with both Baseline and post-Baseline values.

The number and percentage of subjects with newly occurring or worsening notable values, including notable changes from Baseline, will be summarized by vital sign parameter, scheduled post-Baseline visit and treatment group. Subjects with any newly occurring or worsening value meeting the clinically notable criteria will be counted under the applicable

criteria.For a subject to meet the criterion of a newly clinically notable occurrence, the subject needs to have a Baseline value which does not meet the criteria for categorizing a value as notable.For a subject to meet the criterion of a worsening occurrence, the subject needs to have a Baseline value which is clinically notable and also have a worse post-Baseline value.For subjects with a missing value at Baseline, post-Baseline values meeting the notable criterion will be considered as newly occurring. For subjects with both Baseline and post-Baseline values which are clinically notable but in opposing directions (e.g. Low at Baseline and high at post-Baseline, or vice versa), the post-Baseline notable value will be considered as newly occurring.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

See Section 2.7.1.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Not applicable.

3 Sample size calculation

The sample size was calculated based on the primary efficacy variable ASAS40 response at Week 24 for the FAS. Available data from the DESIR cohort (Molto et al 2014) and the DANBIO registry (Glintborg et al 2017) showed an ASAS40 response of 30% in TNFα inhibitor naïve axSpA subjects, that were treated with common *biological* DMARDs.

Data from MEASURE 2/MEASURE 3 trials (Sieper et al 2017, Pavelka et al 2017) showed an ASAS40 response of 43.2% and 43.9% at Week 16, while approximately 50% of subjects did not achieve an ASDAS clinically important improvement (defined as change from BSL of ≥ 1.1) criterion at Week 12. Taking into account the longer duration of active treatment with secukinumab 150 mg and the substantial proportion of subjects that will be escalated to 300 mg, it is justifiable to conservatively assume an ASAS40 response of 50% at Week 24.

With an ASAS40 response of 50% for the secukinumab 150 mg/300 mg arm and a 30% response in the SOC arm at Week 24 (corresponding to an OR of 2.3), 134 subjects per treatment arm are required to achieve a power of 90% to demonstrate superiority at a significance level of 0.05 using the 2-group continuity corrected χ^2 test of equal proportions.

In order to account for some uncertainties in the underlying assumptions and to compensate for some expected dropout and protocol violations, a total of 300 subjects (150 patients in the T2T and 150 patients in the SOC arm) should be randomized into this study.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rules should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1

If the dose end date is completely missing and there is no end of treatment (EOT) page and no death date, the patient is considered as on-going.

The patient should be treated as on-going and the cut-off date should be used as the last dosing date.

Scenario 2

If the dose end date is completely or partially missing and the EOT page is available:

- Case 1: The dose end date is completely missing and the EOT completion date is complete, then this latter date should be used.
- Case 2: Only year (YYYY) of the dose end date is available and YYYY < the year of EOT date, then use 31DECYYYY.
- Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date.
- Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM).

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment.

If the imputed date is < start date of treatment, then use the treatment start date.

Otherwise, use the imputed date.

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE date imputation

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

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

	NON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
YYYY < TRTY	(D) Before Treatment Start	(C) Before Treatment Start	(C) Before Treatment Start	(C) Before Treatment Start
YYYY = TRTY	(B) Uncertain	(C) Before Treatment Start	(A) Uncertain	(A) After Treatment Start
YYYY > TRTY	(E) After Treatment Start	(A) After Treatment Start	(A) After Treatment Start	(A) After Treatment Start

The following table is the legend to the logic matrix.

If AE end date is complete and AE end date < Treatment start date or AE end date is partial and AE imputed end date < Treatment start date, then AE start reference = min (informed consent date, earliest visit date from SV) Else if AE end date is partial,AE end date > = Treatment start date or AE is ongoing , then AE start reference = treatment start date.

Relationship	Time imputation
Before AE start reference	Partial date indicates AE start date prior to AE start reference
After AE start reference	Partial date indicates AE start date after AE start reference
Uncertain	Partial date insufficient to determine relationship of AE start date to AE start reference
Imputation Calculation	
NC/Blank	No convention
(A)	MAX(01MONYYYY, AE start reference+1 day)

Relationship		Time imputation
(B)	AE start reference+1	
(C)	15MONYYYY	
(D)	01JULYYYY	
(E)	01JANYYYY	
Complete date	No date imputation	If time is captured for the study Case1: if AE start date is not equal to AE start reference then do the following: If minutes missing then AESTMF = M and time is imputed to hh:00 If minutes missing then AESTMF = H and time is imputed to 00:00 Case2: if AE start date = AE start reference then AESTMF = H and time is imputed to treatment start time + 1 hour

Adverse Event End Date Imputation

Imputed date = date part of original date, if complete date.

Imputed date = min (completion/discontinuation visit date, DEC 31, date of death), if month is missing.

Imputed date = min (completion/discontinuation visit date, last day of the month, date of death), if day is missing.

Adverse Event End Time Imputation

If the AE end date is complete and time is captured in the study then:

Case 1. If AE end date is not equal to Treatment end date, then do the following:

If minutes missing then time is imputed to hh:00 if time missing then time is imputed to 00:00.

Case 2. If AE end date = Treatment end date then time is imputed to treatment end time.

If the AE end date is partial then end time is imputed to 00:00.

Imputed Date Flag

If year of the imputed date is not equal to YYYY then date flag = Y

else if month of the imputed date is not equal to MON then date flag = M

else if day of the imputed date is not equal to day of original date then date_flag = D

else date flag = null

Imputed Time Flag

If hours of the imputed time is not equal to hours of original time then time flag = H

else if minutes of the imputed time is not equal to minutes of original time then time flag = M else time flag = null.

5.1.3 Concomitant medication date imputation

This algorithm is used when event is the partial start date of the concomitant medication.

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

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

The following matrix explains the logic behind the imputation.

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

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date prior to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date relative to Treatment Start Date
Imputation Calculation	
(A)	15MONYYYY
(B)	01MONYYYY

(C1 or C2)	IF relative reference start = before treatment start THEN TRTSDT-1 ELSE IF relative reference start = ' ' THEN TRTSDT+1
(D)	01JULYYYY
(E)	01JANYYYY

Concomitant Medication End Date Imputation

If not ongoing then:

Imputed date = date part of CMENDTC, if complete date

Imputed date = min(completion/discontinuation visit date, DEC 31) , if month is missing, (C2, D, E)

Imputed date = min(completion/discontinuation visit date, last day of the Month) , if day is missing. (A, B, C1)

Concomitant Medication Date Flag

If not a complete date then

Y - If year of the imputed date is not equal to YYYY else M – If month of the imputed date is not equal to MON else D.

5.1.3.1 Prior therapies date imputation

Same methodology as in Section 5.1.3.

5.1.3.2 Post therapies date imputation

Same methodology as in Section 5.1.3.

5.1.3.3 Other imputations

Same methodology as in Section 5.1.3.

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology. The latest MedDRA version will be used and will be described in the footnote of relevant outputs.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The CTCAE grade of 5 (death)

is not used; rather, "fatal" is collected as AE outcome and death information is also collected on a separate eCRF page.

5.3 Concomitant medication grouping

The following concomitant medications will be categorized by the classes below.

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs)**: Celecoxib, diclofenac, ibuprofen, etoricoxib, meloxicam, naproxen, indometacin, parecoxib, acemetacin, aceclofenac, piroxicam, dexketoprofen, nabumetone, rofecoxib, lornoxicam, diclofenac sodium, ketoprofen, flurbiprofen, piroxicam betadex, sulindac, naproxen sodium, niflumic acid, tenoxicam.

2. Other axSpA medication(s):

Analgesics		
A) Non-opioid	**B) Opioid**	**(C) Other**
Metamizole, metamizole sodium, naloxone hydrochloride, caffeine, papaver somniferum latex, paracetamol, paracetamol, flupirtine maleate, flupirtine maleate	Naloxone hydrochloride;tilidine hydrochloride, codeine, morphine sulfate, codeine phosphate, oxycodone, tramadol, tramadol hydrochloride	Tizanidine hydrochloride, amitriptyline hydrochloride, methocarbamol, amitriptyline, pregabalin, citalopram, methocarbamol

3. DMARDs:

ts DMARDS	**cs DMARDS**		
JAKi	**SS**	**MTX**	**Other**
Upadacitinib	Sulfasalazine	Methotrexate sodium	Leflunomide

4. Biological DMARDs:

(A) alL-17	**(B) TNFi**	**(C) Other**
Secukinumab, ixekizumab	Golimumab, adalimumab, etanercept, certolizumab pegol, infliximab, adalimumab biosimilar	Ustekinumab

5. Glucocorticoids:

(A) Systemic steroids (oral, iv, im)	**(B) Intraarticular steroids**
Prednisolone, cortisone acetate, prednisone, triamcinolone, dexamethasone, prednisolone acetate, cortisone	Cortisone acetate, triamcinolone, prednisolone acetate, triamcinolone hexacetonide

5.4 Laboratory parameters derivations

The table below shows all laboratory parameters that will be presented.

Table 5-1 Laboratory Tests

Order	Laboratory Group Subgroups	Tests [SI unit]
1	Hematology Red Blood Cells	Hematocrit [%] Hemoglobin [mmol/L] Platelet count [10E9/L] Red cell count [10E12/L]
	White Blood Cell Count and Differential	Basophils [%] Eosinophils [%] Lymphocytes [%] Monocytes [%] Neutrophils [%] Absolute Basophils [10E9/L] Absolute Eosinophils [10E9/L] Absolute Lymphocytes [10E9/L] Absolute Monocytes [10E9/L]
2	Clinical Chemistry	Creatinine [umol/L] Blood urea [mmol/L] Albumin [g/L] Alkaline Phosphatase [U/L] Total Bilirubin [umol/L] Total protein [g/L]
	Lipids	Cholesterol HDL [mmol/L] Cholesterol LDL [mmol/L] Triglycerides [mmol/L]
3	Urinalysis	Glucose WBC Occult Blood Protein

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

Hematology variables:

- Hemoglobin: $\geq$ 20 g/L decrease from Baseline

- Platelet count: < lower limit of normal (LLN)
- White blood cell count: < 0.8 × LLN
- Neutrophils: < 0.9 × LLN
- Eosinophils: > 1.1 × ULN
- Lymphocytes: > 1.1 × ULN

5.5 Clinically notable vital signs

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic blood pressure of > 140 mmHg (hypertension)
- Diastolic blood pressure of > 90 mmHg (hypertension)
- Pulse rate > 100 bpm (tachycardia).

Clinically notable below normal values

- Systolic blood pressure of < 90 mmHg (hypotension)
- Diastolic blood pressure of < 60 mmHg (hypotension)
- Pulse rate < 60 bpm (bradycardia)

Worsening clinically notable vital signs

- High pulse rate [bpm]: ≥ 100 bpm with increase from Baseline of ≥ 15 bpm; low pulse rate [bpm]: ≤ 60 bpm with decrease from Baseline of ≥ 15 bpm.
- High systolic blood pressure [mmHg]: ≥ 140 mmHg with increase from Baseline of ≥ 20 mmHg; Low systolic blood pressure [mmHg]: ≤ 90 mmHg with decrease from Baseline of ≥ 20 mmHg.
- High diastolic blood pressure [mmHg]: ≥ 90 mmHg with increase from Baseline of ≥ 15 mmHg; Low diastolic blood pressure [mmHg]: ≤ 60 mmHg with decrease from Baseline of ≥ 15 mmHg.

5.6 Statistical models

5.6.1 SAS code

The below SAS code will used for statistical value.

Frequency and proportion:

```
proc freq data = <........>;
      tables trt*response_variable/ chisq;
run;
```

trt=treatment group

response_variable=Gender, Age group, Race, Country, ASAS40, ASAS20, ASASPR, BASDAI 50 etc.

Summary Statistics:

Univariate procedure will be used for continuous response.

```
proc univariate data=<........>;
       var response_variable;
       by trtn;
       output out=<........> n=_n mean=_mean std=_sd  min=_min median=_med
       max=_max;
run;
```

response_variable= Age, height, weight, bmi etc.

Multivariate logistic regression

```
ods output oddsratios=ratio   parameterestimates=est diffs=diff LSMeans=lsmean;
proc logistic data=<........>;
       class  treatment (ref='1')  center /param=glm;
       model resp1(event='1')= treatment center base_crp base_weight /cl  ;
       oddsratio treatment;
       lsmeans treatment / diff oddsratio cl;
run;
```

Mixed-Effect Model Repeated Measures (MMRM):

```
proc mixed data=<........>;
       class treatment subject visit;
       model chg= treatment  visit base_var weight treatment*visit base_var*visit;
       repeated visit/ subject= subject (treatment ) type=un r rcorr;
       lsmeans treatment*visit / pdiff cl slice=visit;
run;
```

Using the slice option above means that the difference between treatment cohorts will be tested for each visit.

Multiple Imputation

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

```
proc mi data=<xxxxx> out=<impxx> minmaxiter=100000 nimpute=100 seed=4572320;
       by trt;
       var WEIGHT STRATA var1_base var1_week1-var1_week104;
       mcmc chain=multiple initial=em;
run;
```

CM medication categories from CM source dataset

1. NSAIDs

```
CMCAT = 'NONSTEROIDAL ANTI-INFLAMMATORY DRUGS' and
ATC2= 'ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS' and
ATC3= 'ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS';
```

2. Other axSpA medication

```
a) CMCAT = 'OTHER AXIAL SPONDYLOARTHRITIS MEDICATION' and
ATC4 in ('PYRAZOLONES', 'OTHER ANTIMIGRAINE PREPARATIONS', 'ANILIDES')
b) CMCAT = 'OTHER AXIAL SPONDYLOARTHRITIS MEDICATION' and ATC2 = 'ANALGESICS' and
ATC3 = 'OPIOIDS' .
```

```
c) CMCAT = 'OTHER AXIAL SPONDYLOARTHRITIS MEDICATION'
and ATC4 in ('OTHER ANTIMIGRAINE PREPARATIONS', 'OTHER CENTRALLY ACTING AGENTS',
'OTHER ANALGESICS AND ANTIPYRETICS', 'OTHER ANTIMIGRAINE PREPARATIONS', 'SELECTIVE
SEROTONIN REUPTAKE INHIBITORS', 'CARBAMIC ACID ESTERS');
```

3. DMARds

```
a) CMCAT = 'CONVENTIONAL SYSTEMIC DMARD(s)' and ATC4 = 'SELECTIVE
IMMUNOSUPPRESSANTS' and CMSCAT = 'Standard of care of medication_CMS004'.
b) CMCAT = 'CONVENTIONAL SYSTEMIC DMARD(s)' and ATC4 = 'OTHER ANTIINFLAMMATORY AND
ANTIRHEUMATIC AGENTS, NON-STEROIDS'.
c) CMCAT = 'CONVENTIONAL SYSTEMIC DMARD(s)' and ATC4 = 'OTHER IMMUNOSUPPRESANTS'
d) CMCAT = 'CONVENTIONAL SYSTEMIC DMARD(s)'and ATC4 = 'SELECTIVE
IMMUNOSUPPRESSANTS' and CMSCAT = 'Prior axSpa medication_CMS002'.
```

4. bDMARd

```
a) CMCAT = 'BIOLOGICAL DMARD' and ATC4 = 'INTERLEUKIN INHIBITORS'.

b) CMCAT = 'BIOLOGICAL DMARD' and ATC4 = 'TUMOR NECROSIS FACTOR ALPHA (TNF-)
INHIBITORS'.
```

5. Glucocorticodis

```
a)  CMCAT= 'GLUCOCORTICOIDS' and CMROUTE in ('ORAL', 'INTRAMUSCULAR', 'INTRAVENOUS')
and ATC4 = 'GLUCOCORTICOIDS'
b) CMCAT= 'GLUCOCORTICOIDS' and CMROUTE = 'INTRA-ARTICULAR'
```

5.6.2 Key secondary analysis

Not applicable.

6 References

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