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AIN457/Secukinumab

Clinical Trial Protocol 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

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List of abbreviations

AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (Serum Glutamate-Pyruvate Transaminase)
AS	Ankylosing Spondylitis
ASAS	Ankylosing Spondyloarthritis International Society
ASAS-HI	Ankylosing Spondyloarthritis International Societ Health Index
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Chemical
axSpA	Axial Spondyloarthritis
bDMARD	Biological DMARD
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BL	Baseline
CI	Confidence Interval
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRF	Case Report Form
CRP	C-Reactive Protein
CRO	Contract Research Organization
csDMARD(s)	Conventional Systemic DMARD(s)
CV	Cardiovascular
DGRh	German Society of Rheumatology (Detusche Gesellschaft für Rheumatologie e.V.)
DMARD(s)	Disease-Modifying Anti-Rheumatic Drug(s)
eCRF	Electronic Case Report Form
EAM	Extraarticular manifestations
EDC	Electronic Data Capture
EF	Environmental Factor
EMA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
HLA-B27	Human Leukocyte Antigen-B27
hsCRP	High sensitive C-Reactive Protein
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for

	Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IL-17	Interleukin-17
IL-17A	Interleukin-17A
IN	Investigator Notification
IRB	Institutional Review Board
i.v.	Intravenous
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measures
MRI	Magnetic Resonance Imaging
nr-axSpA	Non-Radiographic Axial Spondyloarthritis
NRS	Numeric rating scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PFS	Prefilled Syringe
PR	Partial Remission
PRO(s)	Patient Reported Outcome(s)
PsA	Psoriatic Arthritis
PT	Preferred Term
RA	Rheumatoid Arthritis
RAS	Randomized Analysis Set
r-axSpA	Radiographic Axial Spondyloarthritis
RMP	Risk Management Plan
SAE	Serious Adverse Event
s.c.	Subcutaneous
SF-36	Short Form Health Survey
SIB	Suicidal Ideation and Behavior
[redacted]	[redacted]
SOC	Standard-of-Care
SpA	Spondyloarthritis
TB	Tuberculosis
T2T	Treat-to-Target
[redacted]	[redacted]
TNFα	Tumor Necrosis Factor Alpha
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy).
Assessment	A procedure used to generate data required by the study.
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study patient.
DMARDs	Disease modifying anti-rheumatic drugs. This drug class includes biological DMARDs (bDMARDs) and conventional systemic DMARDs (csDMARDs).
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 300 mg every 4 weeks).
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last patient or at a later point in time as defined by the protocol.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained.
Investigational drug/treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.
Mis-randomized patients	Mis-randomized patients are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy).
Patient	An individual with the condition of interest for the study.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized patient.
Screen failure	A patient who did not meet one or more criteria that were required for participation in the study.
Source data/document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first patient.

Study treatment	Any single drug or combination of drugs or intervention administered to the patient as part of the required study procedures.
Study treatment discontinuation	When the patient permanently stops taking any of the study drugs prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation.
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data.

Amendment rationale

The protocol including amendment 1 is being amended to delete the planned IA that became obsolete due to availability of secukinumab data that fully supports the assumptions for initial sample size calculation.

The sample size was calculated based on the primary efficacy variable ASAS40 response at Week 24. At the time point of the conception of the AScalate study, no data on effect of secukinumab in patients with non-radiographic spondyloarthritis, or data on direct secukinumab escalation from 150 mg to 300 mg was available. Therefore data on secukinumab efficacy (150 and/or 300 mg treatment) from trials with ankylosing spondylitis patients (MEASURE 2/MEASURE 3 trials (Sieper et al 2017, Pavelka et al 2017) was taken as a basis for estimation of the effect size of treatment in treat-to-target arm. In order to confirm the assumption for the sample size calculation an interim analysis for the study has been planned.
Recently, new data on secukinumab dose escalation in AS patients became available (Novartis data on file), furthermore PREVENT study[1] showed secukinumab efficacy in nr-axSpA patients be comparable to its efficacy in AS patients.
This novel data confirms assumptions used as a basis for initial sample size calculation, making the planned interim analysis obsolete.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red font for insertions.

- **Cover page** information has been updated as well as document version number in **headers** on each page of the protocol
- **Protocol summary:**
  - IA details have been deleted in 'data analysis' section
- **Section 4.4:** information regarding the interim analysis have been deleted
- **Section 12.7:** information regarding the interim analysis have been deleted
- **Section 15:** reference regarding the interim analysis has been deleted

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment rationale

The main purpose of this amendment is to incorporate two novel components into the protocol for the following reasons:

[redacted]

None of the changes made are due to evidence-based safety concerns.

Changes to the protocol:
Changes to specific sections of this protocol are shown in the track changes version of the document using ~~strike through red~~ font for deletions and red underlined font for insertions.

- **Cover page** information has been updated as well as document version number in **headers** on each page of the protocol
- **List of abbreviations:** addition of baseline (BL) and numeric rating scale (NRS)
- **Protocol summary:**
  - [redacted]
  - refinement of inclusion criteria 5
- **Introduction – Background:** [redacted]
- **Section 2:** [redacted]
- **Section 4.1:** [redacted]
- **Section 5.1:** refinement of inclusion criteria 5
- **Section 5.2:** 'Laboratory results at screening visit' was added for clarification

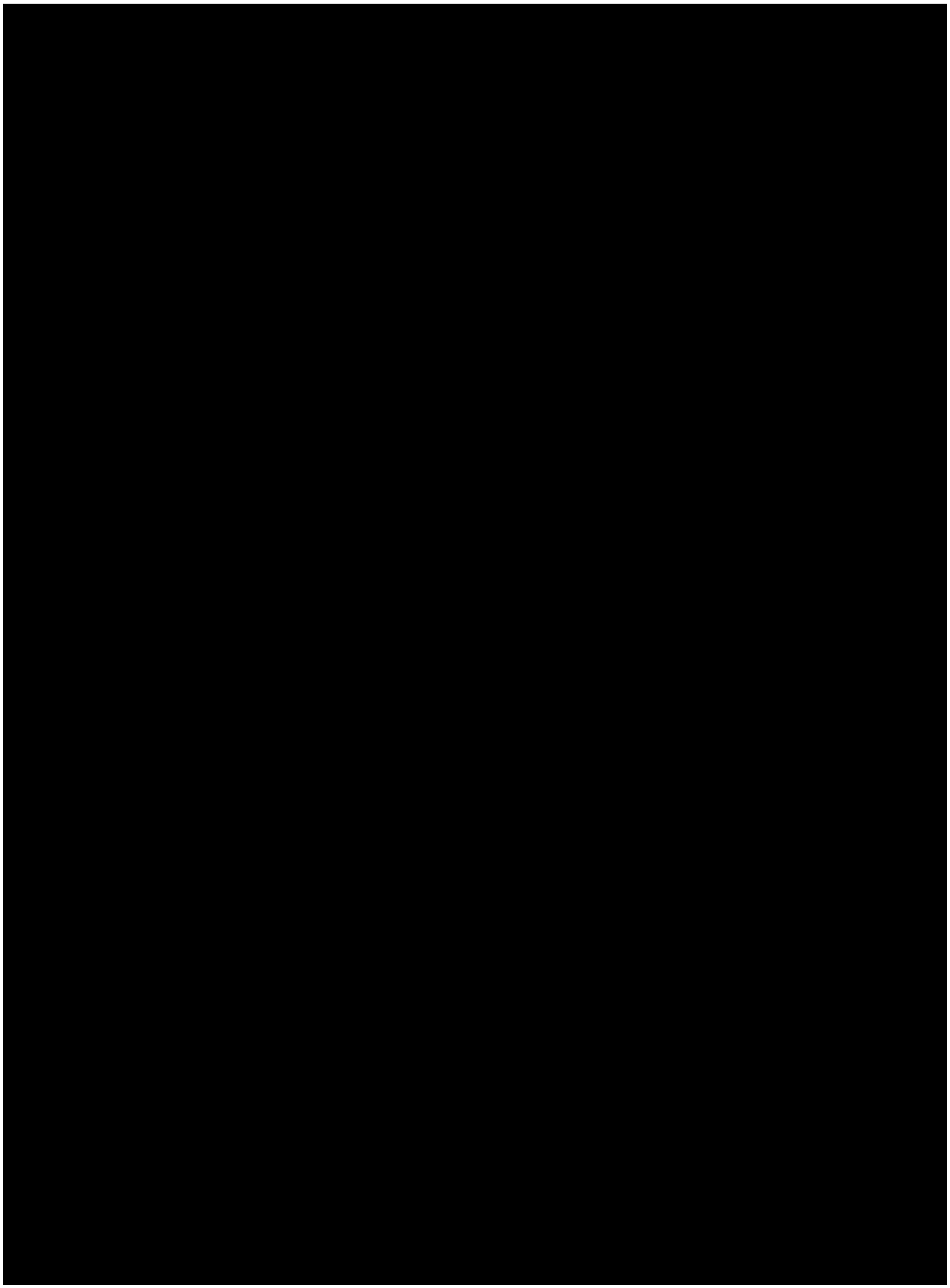
- **Section 6.2.2 – Table 6-1:** addition of medical cannabis to prohibited prior medication table and clarification of amount of corticosteroids as per day
- **Section 6.2.2.2 – Table 6-2:** addition of medical cannabis use and correction of algebraic sign and additional information added to corticosteroids criteria
- **Section 6.3.1:** removal incomplete sentence
- **Section 6.6.1:** added defined tolerance levels regarding allowed visit/treatment windows
- **Section 6.7.2:** updated handling instructions because packaging label cannot be attached to the drug label form
- **Section 8 – Table 8-1:**
  - [redacted]
  - updated footnote number 6 to reflect refined inclusion criteria 5
- **Section 8.2.2.9:** corrected BL to SV2 to ensure consistency throughout the protocol
- **Section 8.5.2:** [redacted]
- **Section 8.5.3:** section was added to provide detailed information regarding the companion app implementation
- **Section 8.5.4:** [redacted]
- **Section 12.4.1:** removed unnecessary word to clarify
- **Section 12.5.1:** corrected spelling error
- **Section 12.6:** [redacted]
- **Section 15:** additional reference inserted
- **Section 16.8:** corrected spelling error

Protocol summary

Protocol number	CAIN457HDE01
Full title	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
Brief title	Efficacy of a treat-to-target strategy with first-line secukinumab compared to standard-of-care in patients with active axSpA
Sponsor and clinical phase	Novartis Pharma GmbH, Phase IIIb
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The standard treatment approach in axSpA is to start with one non-steroidal anti-inflammatory drug (NSAID), switch to another one if the first one is not effective enough, and, if the second one also fails, start a biological disease modifying anti-rheumatic drug (bDMARD). According to the 2016 updated Ankylosing SpondyloArthritis International Society (ASAS)/European League Against Rheumatism recommendations, current practice is to start biological therapy with a tumor necrosis factor alpha (TNFα) blocker; however, based on indirect comparisons the efficacy of TNFα and interleukin-17A (IL-17A) blockade seems to be similar. In case of failure of the first bDMARD, a switch within the class or between classes of biological drugs is possible, but there is not enough evidence to support either strategy. The purpose of the study is to demonstrate superiority of the intensive treat-to-target (T2T) strategy with secukinumab as first-line biologic vs. standard-of-care (SOC) therapy in order to achieve strong clinical efficacy in patients with active axSpA inadequately responding to NSAID therapy. AxSpA includes radiographic axSpA (r-axSpA), also known as ankylosing spondylitis (AS), and non-radiographic-axSpA (nr-axSpA).
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 patients achieving an ASAS 40% response (ASAS40) at Week 24.
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 patients 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 patients achieving an AS Disease Activity Score (ASDAS) clinically important improvement (defined as change from Baseline 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 BL 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 patients 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 patients achieving ASDAS < 2.1 (low disease activity) 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 patients achieving ASAS 20% response (ASAS20), ASAS partial remission (PR), and Bath Ankylosing Spondylitis Disease Activity Index 50% response (BASDAI50) 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:
	  • BASDAI
	  • ASDAS
	  • C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
	  • Bath ankylosing spondylitis functional index (BASFI)
	  • Bath ankylosing spondylitis metrology index (BASMI) and chest expansion
	  • Global assessment of disease activity (patient/physician) and general pain on visual analog scale (VAS)
	  • ASAS health index (ASAS-HI)
	  • Short form health survey (SF-36)
	  • Ankylosing spondylitis quality of life (ASQoL)
	  • Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-Fatigue)
	• To demonstrate overall safety and tolerability of secukinumab.

[redacted]	



[redacted]

Study design	This is a randomized, parallel-group, open-label, multicenter study of patients with active axSpA. The aim is to demonstrate that the efficacy of a T2T approach (with secukinumab as first-line biologic) is superior to a SOC approach in terms of achieving strong clinical efficacy in patients with active axSpA who are naïve to biological therapy and who have had an inadequate response to NSAID treatment. The study will include an 8-week Screening period, a 36-week treatment period according to previous randomization, and a safety follow-up period of 20 weeks. Neither investigators nor patients will be blinded. The primary endpoint is the percentage of patients achieving an ASAS40 response at Week 24.
Population	The study population will consist of approximately 300 patients fulfilling the ASAS classification criteria for axSpA with active disease (measured by ASDAS ≥ 2.1 and elevated CRP and/or active inflammation on MRI of the sacroiliac joints and/ or spine) inadequately responding to or with intolerance/contraindications for NSAIDs, and with no previous treatment with a biological drug.
Inclusion criteria	Patients eligible for inclusion in this study must fulfill all of the following criteria: 1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent before any study assessment is performed. 2. Male or non-pregnant, non-lactating female patients at least 18 years of age. 3. Diagnosis of axSpA (either r-axSpA (AS) or nr-axSpA) fulfilling the ASAS classification criteria for axSpA (see Appendix 2 of main protocol). 4. Active disease as defined by having an ASDAS ≥ 2.1 at Screening and Baseline despite concurrent NSAID therapy, or intolerance/contraindication to NSAIDs. 5. Objective signs of inflammation at Screening as defined by: • MRI of sacroiliac joints performed up to 3 months prior to screening showing acute inflammatory lesion(s), OR • elevated quick CRP (> 5 mg/L), OR • MRI showing acute inflammatory lesion(s) in the sacroiliac joints performed during screening period. 6. Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks (in total) in the past, with an inadequate response or failure to respond, or less if therapy had to be reduced due to intolerance, toxicity or contraindications. 7. Patients who are regularly taking NSAIDs (including cyclooxygenase-1 [COX-1] or cyclooxygenase-2 [COX-2] inhibitors) as part of their axSpA therapy are required to be on a stable dose for at least 1 week before randomization.

	8. Patients taking methotrexate (MTX) 7.5 mg/week to 25 mg/week or sulfasalazine (≤ 3 g/day) are allowed to continue their medication but are required to be on a stable dose for at least 4 weeks before randomization. 9. Patients who are on a disease modifying anti-rheumatic drug (DMARD) other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization. 10. Patients taking corticosteroids must be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization.
Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients. 1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician. 2. Previous exposure to secukinumab or other biologic drug directly targeting interleukin-17 (IL-17) or IL-17 receptor. 3. Patients who have previously been treated with TNFα inhibitors (investigational or approved). 4. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine). 5. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. CAMPATH, anti-CD3, anti-CD4, anti-CD5, anti-CD19). 6. History of hypersensitivity to secukinumab or adalimumab or their excipients or to drugs of similar chemical classes. 7. Contraindications for secukinumab or adalimumab. 8. Inability or unwillingness to undergo MRI (e.g. patients with pacemakers, aneurysm clips or metal fragments / foreign objects in the eyes, skin or body that are not MRI compatible) in case MRI is not already available (maximum 3 months old). 9. Use of any investigational agents within 4 weeks or within 5 half-lives of the drug (whichever is longer) prior to the Baseline Visit. 10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in the European Union). Effective contraception methods include: • Total abstinence* (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

	• Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. • Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient. • Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). • Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device or intrauterine system. *Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug. In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF). Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child-bearing potential. 12. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis. 13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy. 14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes. 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase or serum bilirubin. The investigator should

	be guided by the following criteria: a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible laboratory error. b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. 16. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 µmol/L). 17. Screening total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1500/µL or hemoglobin < 8.3 g/dL (83 g/L). 18. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization. 19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis (TB) infection as defined by a positive QuantiFERON TB-Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment according to local country guidelines must have been initiated prior to randomization. 20. Patients positive for human immunodeficiency virus, hepatitis B or hepatitis C at randomization. 21. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 22. Live vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration. 23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial. 24. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins). 25. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol. 26. Donation or loss of 400 mL or more of blood within 8 weeks before randomization. 27. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization.
Study treatment	**Investigational treatment – treat-to-target regimen** • Secukinumab 150 mg, liquid formulation in 1 mL prefilled syringe (PFS) for subcutaneous (s.c.) injection – all patients will receive 150

	mg dose at Baseline, Week 1, 2, 3, 4 and 8. From Week 12, only responders (i.e. patients with ASDAS clinically important improvement, defined as change from Baseline ≥ 1.1) will continue to receive 4-weekly doses until Week 32 if they maintain the response. • Secukinumab 300 mg, liquid formulation in 2 × 1 mL PFS for s.c. injection – patients who are non-responders at Week 12 will receive 4-weekly doses until Week 24. From Week 24, only responders will continue to receive 4-weekly doses until Week 32. • Adalimumab biosimilar (Hyrimoz®) 40 mg, liquid formulation in 0.8 mL PFS for s.c. injection – patients who are non-responders to secukinumab 300 mg only at Week 24 will receive biweekly doses of adalimumab biosimilar (Hyrimoz®) until Week 34. • Escape treatment: Secukinumab 300 mg liquid formulation in 2 × 1 mL PFS for s.c. injection. Patients who are receiving secukinumab 150 mg (i.e. were responders at Week 12) can be escalated to secukinumab 300 mg at Week 24 every 4 weeks until Week 32 if they experienced a loss of response (defined as ASDAS change from Baseline < 1.1). **Reference treatment – standard-of-care regimen** • SOC treatment up to the maximum recommended dose at the discretion of the investigator as according to current recommendation for treatment of axSpA.
Efficacy assessments	**Primary endpoint** • Percentage of patients achieving an ASAS40 response at Week 24. **Secondary endpoints** • Percentage of patients achieving an ASAS40 response at Week 12. • Percentage of patients achieving an ASDAS clinically important improvement (defined as change from BL of ≥ 1.1) at Week 12 and Week 24. • Percentage of patients achieving an ASDAS major improvement (defined as change from BL of ≥ 2.0) at Week 12 and Week 24. • Percentage of patients achieving ASDAS < 1.3 at Week 12 and Week 24. • Percentage of patients achieving ASDAS < 2.1 (low disease activity) at Week 12 and Week 24. • Percentage of patients achieving ASAS20, ASAS PR, BASDAI50 responses at Week 12 and Week 24. • 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

	○ ASAS-HI ○ SF-36 ○ ASQoL ○ FACIT-Fatigue

Safety assessments	• The number (and percentage) of patients with treatment-emergent AEs.
[redacted]	
Data analysis	The primary analysis will be performed comparing treatments with

	respect to the primary efficacy variable (i.e. the proportion of patients achieving treatment response as defined by the ASAS40 criteria at Week 24) in a logistic regression model with treatment and center as factors and weight as well as Baseline CRP level as covariates. The odds ratio (OR), the corresponding 95% confidence interval (CI) and the p-value will be given. The null hypothesis of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor “treatment” is < 0.05. Sensitivity analyses as well as supportive analyses will be conducted in order to provide evidence that the results seen from the primary model results are robust. These analyses will center on the deviations in model assumptions and the treatment of missing data.
Key words	Secukinumab, axSpA, ASAS, ASDAS, treat-to-target

1 Introduction

1.1 Background

Axial Spondyloarthritis (axSpA) is a group of rheumatic disorders with spinal inflammation and inflammatory back pain as common denominator. Based on the presence or absence of sacroiliitis on conventional radiographs, axSpA patients are sub-grouped into non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS) also termed radiographic axSpA (r-axSpA). Although nr-axSpA is often regarded as a milder disease compared to AS/r-axSpA, it has been demonstrated that the burden of the 2 diseases is similar in terms of symptom levels (Poddubnyy and Sieper 2014, Sieper et al 2013).

For patients with active r-axSpA (AS), effective therapeutic options are currently limited to 3 drug classes. These are non-steroidal anti-inflammatory drugs (NSAIDs), tumor necrosis factor alpha (TNFα) blockers, and interleukin-17A (IL-17A) inhibitors. In the IL-17A inhibitor class, only 1 substance, secukinumab, the investigational product in this study, is approved for the treatment of patients with active r-axSpA (AS). Secukinumab, a human monoclonal antibody that inhibits the effector function of IL-17A, has been shown to be better than placebo in improving the signs and symptoms of AS. In the Phase III MEASURE 1 (Braun et al 2017) and MEASURE 2 studies (Sieper et al 2017) involving a total of 590 patients with AS, secukinumab significantly improved key clinical domains of disease vs. placebo, including signs and symptoms, physical functioning, and quality of life (Baeten et al 2015). Interim results of the ongoing MEASURE-3 study (involving 226 patients) assessing the efficacy and safety of s.c. maintenance therapy with secukinumab 150 mg and 300 mg following intravenous (i.v.) loading have demonstrated rapid and significant improvements in the signs and symptoms of active AS with responses sustained through 104 weeks (Pavelka et al 2017) (see Section 4.2 for further details). Secukinumab has been implicated to mediate early pain relief in patients suffering from AS. In this present study, patient's pain diaries will be used to gather detailed insights into the alteration of pain status, especially during the early stages of treatment. Additionally, a digital option (companion app) will be offered to patients to track their health status over time on their mobile phone.

For patients with active axSpA the main treatment aim according to the recently updated treat-to-target (T2T) recommendation is remission (Smolen et al 2018). The initial treatment approach in axSpA is straightforward: start with one NSAID, switch to another one if the first one is not effective enough, and, if the second one also fails, start a biological disease modifying anti-rheumatic drug (bDMARD). According to the 2016 updated Ankylosing SpondyloArthritis International Society (ASAS)/European League Against Rheumatism recommendations, current practice is to start biological therapy with a TNFα blocker (van der Heijde et al 2017); however, based on indirect comparisons, the efficacy of TNFα and IL-17A blockade seems to be similar (Maksymowych et al 2017). In case of the failure of the first bDMARD, a switch within the class or between classes is possible, but again, there is not enough evidence to support either strategy.

Indeed, many questions related to the optimal treatment strategy remain: What is the optimal first biologic drug in axSpA? Could the introduction of a biologic therapy combined with tight disease control rapidly lead to beneficial effects? Could dosage escalation of an IL-17A

blocker in patients that did not reach Ankylosing Spondylitis Disease Activity Score (ASDAS) clinically important improvement criterion lead to the achievement of that goal? Would a TNFα inhibition after IL-17A inhibitor treatment be beneficial to patients? In order to answer these questions a randomized controlled study is proposed.

1.2 Purpose

The purpose of this study is to provide 36-week efficacy data on a T2T approach with secukinumab as first line biologic compared with the standard-of-care (SOC) approach in patients with active axSpA who have an inadequate response to NSAID therapy in order to confirm that such a T2T approach results in superior efficacy compared to the SOC approach, thereby providing an optimal treatment strategy for this patient population.

2 Objectives and endpoints

Table 2-1 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 patients achieving an ASAS40 response at Week 24.	• Percentage of patients 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 patients achieving an ASAS40 response at Week 12.	• Percentage of patients 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 patients achieving an ASDAS clinically important improvement (defined as change from BL of ≥ 1.1) at Week 12 and Week 24.	• Percentage of patients achieving an ASDAS clinically important improvement (defined as change from BL 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 BL of ≥ 2.0) at Week 12 and Week 24.	• Percentage of patients achieving an ASDAS major improvement (defined as change from BL 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 patients achieving ASDAS < 1.3 at Week 12 and Week 24.	• Percentage of patients achieving ASDAS < 1.3 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 patients achieving ASDAS < 2.1 (low disease activity) at Week 12 and Week 24.	• Percentage of patients achieving ASDAS < 2.1 (low disease activity) 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 patients achieving ASAS20, ASAS PR, and BASDAI50 responses at Week 12 and Week 24.	• Percentage of patients achieving ASAS20, ASAS PR, BASDAI 50 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 CRP and ESR o BASFI o BASMI and chest expansion o Global assessment of disease activity (patient/physician) and general pain on VAS o ASAS-HI o SF-36 o ASQoL o 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 AEs.

[redacted]

Objectives	Endpoints
[redacted]	

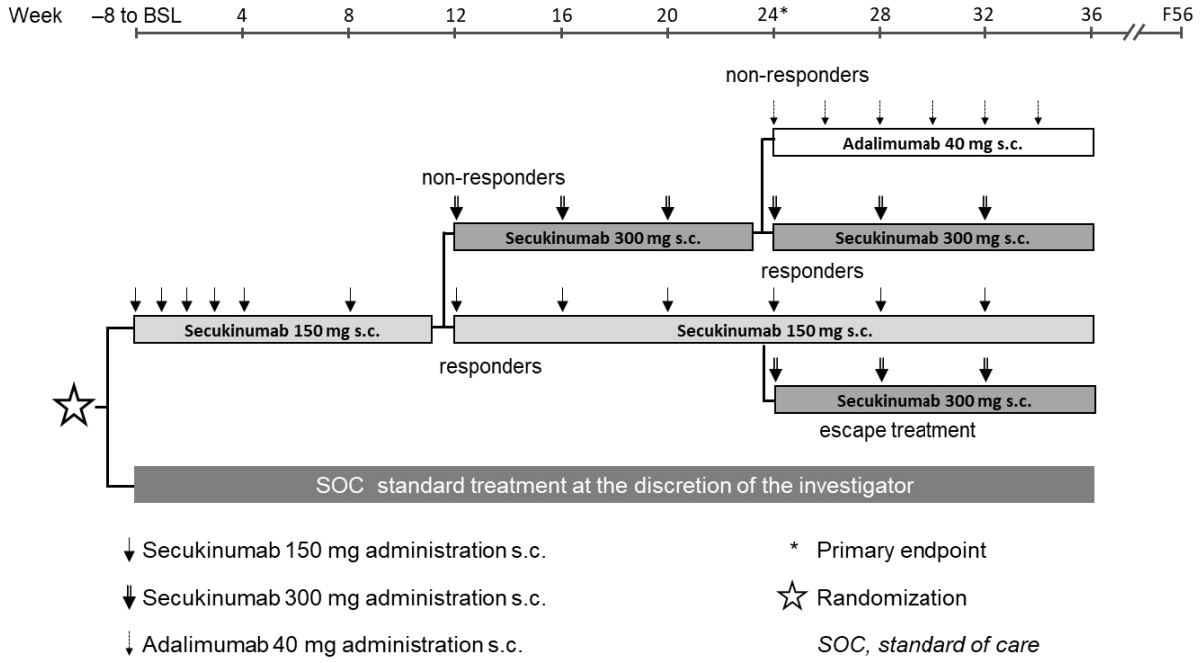
Objectives	Endpoints
[redacted]	

ASAS=Ankylosing SpondyloArthritis International Society, ASDAS=AS disease activity score, ASQoL=ankylosing spondylitis quality of life, BASDAI=Bath ankylosing spondylitis disease activity index, BASFI=Bath ankylosing spondylitis functional index, BASMI=Bath ankylosing spondylitis Metrology Index, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, FACIT-Fatigue=functional assessment of chronic illness therapy – fatigue, [redacted] MRI=magnetic resonance imaging, PR= partial remission, SF-36=Short form health survey, SOC=standard-of-care, VAS=visual analog scale

3 Study design

This is a randomized, parallel-group, open-label, multicenter study in patients with active axSpA. The aim of the study is to demonstrate that the efficacy of a T2T approach (with secukinumab as a first-line biologic) is superior to a 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 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 patients will be blinded. The primary endpoint is the percentage of patients achieving an ASAS40 response at Week 24. At Baseline, patients will be randomized equally to one of 2 treatment groups (T2T or SOC) as shown in Figure 3-1:

Figure 3-1 Study design



Patients 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 patients completing the study according to the protocol. In addition, patients in the T2T arm will be seen for safety monitoring at Visit 4 (Week 4) and Visit 5 (Week 8). Patients 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.

T2T group (n = 150)

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

At Week 12:

- If ASDAS clinically important improvement is achieved (i.e. patient is a responder) and maintained, patient will continue the treatment with secukinumab 150 mg s.c. every 4 weeks up to Week 32.
- If ASDAS clinically important improvement is not achieved (i.e. patient is non-responder), patient will receive an escalated dose of secukinumab 300 mg s.c. every 4 weeks until Week 20.

At Week 24:

Patients who are receiving secukinumab 300 mg, and

- Achieved ASDAS clinically important improvement (i.e. are responders), will continue treatment with secukinumab 300 mg s.c. every 4 weeks up to Week 32.
- Did not achieve ASDAS clinically important improvement (i.e. are non-responders), will be switched to adalimumab biosimilar (Hyrimoz®) 40 mg s.c. every 2 weeks until Week 34.

Escape arm

- Patients 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.

SOC group (n = 150)

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 despite the use (or intolerance/contraindication) of 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 [redacted].

4 Rationale

4.1 Rationale for study design

A randomized, parallel-group, open-label, multicenter study design is considered appropriate for assessing whether a T2T approach with secukinumab as a first-line biologic confers superior efficacy to a SOC approach for patients with active axSpA as measured primarily based on the percentage of patients with an ASAS40 response at Week 24. All patients included in this study must have active disease despite concurrent NSAID therapy or intolerance/contraindication to NSAIDs. [redacted]

Patients assigned to the SOC treatment group will receive SOC treatment at the discretion of the Investigator in accordance with current clinical practice.

Patients assigned to the T2T treatment group will receive first line biological treatment with secukinumab 150 mg. Responders are defined as those patients with an ASDAS clinically important improvement of ≥ 1.1. At Week 12, responders will continue secukinumab 150 mg through to Week 32 if they maintain the response, and non-responders will be switched to secukinumab 300 mg through to Week 20. At Week 24, responders will continue secukinumab 300 mg through to Week 32 and non-responders will be switched to

adalimumab biosimilar (Hyrimoz®) 40 mg through to Week 34. In addition, patients who were responders at Week 12 but experienced a loss of response (defined as ASDAS change from Baseline < 1.1) at Week 24 will be switched to an escape arm and treated with secukinumab 300 mg through to Week 32. This T2T approach will ensure patients have maximal opportunity to achieve remission.

4.1.1 Bias-reducing measures

In order to avoid selection bias in this study, patients will be randomized to the two treatment groups. All study sites will be provided with a set of sealed allocation cards. At the Randomization Visit, the investigator will assign each patient who meets the study eligibility criteria to the lowest available randomization number, open the corresponding treatment allocation card and treat the patient with the treatment noted on the card (i.e. T2T treatment or SOC treatment).

As blinding of site personnel and patients is not possible in practice for the chosen study design, there is a risk of performance bias. Performance bias refers to systematic differences between groups in the care that is provided. To ensure the control of performance bias, the assessments (timing of study visits, patient and physician disease activity checks and outcomes, etc.) in both treatment groups are identical, with the exception of additional blood samples at Week 4 and Week 8, which are required for secukinumab as per German Society of Rheumatology (Deutsche Gesellschaft für Rheumatologie e.V. - DGRh) recommendations (Table 8-1).

The treatment in T2T arm and in SOC arm is described in detail in Section 6.1. The treatment in the SOC arm will follow the clinical routine of the investigator and should be in accordance with current guidelines for treatment of axSpA (van der Heijde et al 2017). All investigators will be trained on the specifics of treating patients that receive the standard-of-care regimen. In addition, current EULAR guidelines for treatment of axSpA will be provided to all study sites. The clinical monitoring team, who are educated in current treatment guidelines, will check site adherence to these guidelines during the regular monitoring visits. Reasons for non-adherence will be investigated and documented properly. Furthermore, the necessity of adherence to guidelines will be emphasized to investigators.

4.2 Rationale for dose/regimen and duration of treatment

The secukinumab dosing regimens in this study are based upon the currently approved dose for r-axSpA (AS) by the European Medicines Agency (EMA), which is 150 mg s.c. every 4 weeks (with a loading dosage of 150 mg at Week 0, 1, 2, 3, and 4), as well as the 300 mg s.c. dose every 4 weeks (with a loading dosage of 300 mg at Week 0, 1, 2, 3, and 4), which is approved by the EMA for plaque-psoriasis and psoriatic arthritis (PsA). The higher dose (300 mg) has also been reported to be safe and effective when used up to 104 weeks in patients with ax-SpA in the interim analysis (IA) of the ongoing MEASURE-3 study (Pavelka et al 2017).

The approval of secukinumab in AS was based on evaluation of 590 patients with AS in 2 randomized, double-blind, placebo-controlled phase III studies (MEASURE-1: Braun et al 2017, and MEASURE-2: Sieper et al 2017), in which 75 mg and 150 mg were evaluated vs. placebo with either an i.v. or s.c. loading regimen. In MEASURE-1 and MEASURE-2, 27.0%

and 38.8% of patients, respectively, were previously treated with an anti-TNFα agent and discontinued the anti-TNF-α agent due to either lack of efficacy or intolerance (anti-TNFα-inadequate responder [IR] patients).

In MEASURE-2, treatment with secukinumab150 mg resulted in greater improvement in ASAS20 (61.1% vs. 28.4%), ASAS40 (36.1% vs. 10.8%), as well as in high-sensitivity C-reactive protein (hsCRP), ASAS 5/6 and bath ankylosing spondylitis disease activity index (BASDAI) score compared with placebo at Week 16. The onset of action of secukinumab 150 mg occurred as early as Week 1 for ASAS20 (superior to placebo) in MEASURE-2. ASAS20 responses were improved at Week 16 in both anti-TNFα-naïve patients (68.2% vs. 31.1%; $p < 0.05$) and anti-TNFα-IR patients (50.0% vs. 24.1%; $p < 0.05$) for secukinumab 150 mg compared with placebo, respectively. The magnitude of response (treatment difference vs. placebo) with regards to signs and symptoms at Week 16 was similar in anti-TNFα-naïve and anti-TNFα-IR patients in both studies.

In MEASURE-2, secukinumab-treated patients reported improvements compared to placebo-treated patients in tiredness (fatigue) as reported at Week 16 by scores on the functional assessment of chronic illness therapy - fatigue (FACIT-Fatigue) scale and in health-related quality of life as measured by short form health survey (SF-36) physical component summary (PCS) (LS mean change: 6.06 vs. 1.92, $p < 0.001$). These improvements were sustained up to Week 52. In MEASURE-1, secukinumab-treated patients reported improvement in physical function compared to placebo-treated patients at Week 16, as assessed by the FACIT-Fatigue, EQ-5D and SF-36 PCS. These improvements in physical function were all sustained up to Week 52.

Interim results of the ongoing MEASURE-3 study (involving 226 patients) (Pavelka et al 2017) assessing the efficacy and safety of s.c. maintenance therapy with secukinumab 150 mg and 300 mg following i.v. loading have shown that secukinumab provided rapid and significant improvements in the signs and symptoms of active AS, with responses sustained through 104 weeks. Secukinumab was well-tolerated with a safety profile consistent with previous reports. The primary endpoint was ASAS20 response rate at Week 16. Secondary endpoints included ASAS40, high sensitivity CRP, ASAS 5/6, BASDAI and ASAS partial remission (PR). Analyses by prior anti-TNF therapy use (anti-TNF-naïve and -inadequate response or intolerance) were pre-specified and reported as observed at Week 104.

A total of 84.2% (64/76; secukinumab i.v.→300 mg) and 77.0% (57/74; secukinumab i.v. →150 mg) of patients completed 104 weeks of treatment at the time of the IA. The ASAS20 response rate was significantly greater at Week 16 (primary endpoint) in secukinumab i.v.→300 mg and i.v.→150 mg groups compared to placebo. All secondary endpoints were met at Week 16, except ASAS PR in the i.v.→150 mg group. Improvements achieved with secukinumab in all clinical endpoints at Week 16 were sustained through Week 104. ASAS20/40 and ASAS PR responses by anti–TNF status are shown in Table 4-1. At Week 104, response rates on more stringent clinical endpoints (e.g. ASAS PR) were higher with the 300 mg dose, particularly in the smaller group of anti–TNF-IR pts. Safety profiles of both secukinumab doses were similar through Week 104 (mean ± SD exposure: 633.8 ± 165.4 days [300 mg] and 644.5 ± 135.4 days [150 mg]).

Table 4-1 Summary of efficacy results at Week 16 and Week 104 – MEASURE-3 by overall population

Variable	Week	Secukinumab 10 mg/kg IV→ 300 mg SC (N = 76)	Secukinumab 10 mg/kg IV → 150 mg SC (N = 74)	Placebo (N = 76)
ASAS20[a], n (%)	16	46 (60.5)§	43 (58.1)‡	28 (36.8)
	104	55 (72.1)	54 (73.6)	-
ASAS40[a], n (%)	16	32 (42.1)‡	30 (40.5)‡	16 (21.1)
	104	42 (55.7)	36 (49.2)	-
hsCRP[b] (post-baseline/baseline ratio), mean change from baseline ± SE	16	0.48 ± 1.1‡	0.55 ± 1.1‡	1.09 ± 1.1
	104	0.50 ± 1.1	0.59 ± 1.1	-
ASAS5/6[a], n (%)	16	30 (39.5)‡	31 (41.9)‡	11 (14.5)
	104	42 (54.9)	37 (50.0)	-
BASDAI[b], mean change from baseline ± SE	16	-2.7 ± 0.3‡	-2.3 ± 0.3‡	-1.5 ± 0.3
	104	-3.3 ± 0.3	-3.0 ± 0.3	-
ASAS[a] PR, n (%)	16	16 (21.1)‡	7 (9.5)	1 (1.3)
	104	20 (25.7)	13 (18.2)	-

By anti–TNFα status[c]

		Anti–TNF-naïve			Anti–TNF-IR		
Variable, % responders	Week	IV→ 300 mg (N = 57)	IV→ 150 mg (N = 57)	Placebo (N = 59)	IV→ 300 mg (N = 19)	IV→ 150 mg (N = 17)	Placebo (N = 17)
ASAS20	16	64.9§	63.2‡	39.0	47.4	41.2	29.4
	104*	78.4	80.4	-	84.6	54.5	-
ASAS40	16	43.9‡	43.9‡	23.7	36.8	29.4	11.8
	104*	64.7	56.5	-	61.5	27.3	-
ASAS PR	16	21.1§	10.5	1.7	21.1	5.9	0
	104*	31.4	26.1	-	23.1	0	-

§P < 0.01; ‡P < 0.05 vs. placebo (P-values at Week 16 adjusted for multiplicity of testing in overall population)

[a]NRI at Week 16 and multiple imputation at Week 104

[b]Mean changes from MMRM

[c]NRI at Week 16 and observed data at Week 104.

*Total number of evaluable pts in anti–TNF-naïve: IV→ 300 mg= 51, IV→ 150 mg = 46, and in anti–TNF-IR: IV→ 300 mg= 13, IV→ 150 mg = 11

ASAS, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index;
hsCRP, high sensitivity C-reactive protein; n, number of pts meeting criteria; N, number of randomized pts; PR, partial remission; SE, standard error

Source: Pavelka et al 2017

4.3 Rationale for choice of second biological treatment in the treat-to-target group, and for reference treatment

Adalimumab has been selected as the second bDMARD for the T2T approach (in case of insufficient response to secukinumab treatment at Week 24) as this is a commonly used anti-TNFα agent, approved for the treatment of patients with AS /axSpA, and which confers similar efficacy to secukinumab in terms of signs and symptoms (van der Heijde et al 2006).

The reference treatment in this study will be SOC treatment for axSpA. Patients assigned to the SOC treatment arm will receive treatment according to local practice standards by their treating rheumatologist following the current treatment recommendations with NSAIDs as the first-choice drug treatment and DMARDs for patients with active disease despite the use (or intolerance/contraindication) of NSAIDs.

4.4 Risks and benefits

As of 25-Jun-2018, approximately 24279 subjects (which included patients and a small number of healthy volunteers) were enrolled in the secukinumab clinical development program (including trials where secukinumab had been used as a protocol specified treatment), of whom approximately 20000 subjects (comprised of patients and healthy volunteers) had received at least 1 dose of secukinumab. Overall, healthy subjects and patients suffering from psoriasis, PsA, rheumatoid arthritis (RA), AS (r-axSpA), nr-axSpA, multiple sclerosis, uveitis, dry eye, Crohn's disease, asthma and *polymyalgia rheumatica* have received secukinumab at doses ranging from single and multiple i.v. doses of 0.1 mg/kg up to 30 mg/kg and s.c. doses of 25 mg up to 300 mg. The cumulative patient exposure since the first launch of secukinumab is estimated to be approximately 212060 patient years.

Full safety results from all PsA, AS (r-axSpA) and psoriasis completed studies show that secukinumab generally is safe and well tolerated.

The safety profile observed in the latest drug safety update report (Issue 008: 26-Jun-2017 to 25-Jun-2018) is in line with the current known safety profile of secukinumab in moderate to severe psoriasis, PsA and AS.

For all 3 indications, secukinumab has shown an imbalance vs. placebo in total adverse events (AEs), which was driven by infections, mainly non-serious upper respiratory tract infections during the placebo-controlled epoch of the trials (12 to 16 weeks depending on the protocol). This imbalance was not translated into infection serious adverse events (SAEs) and there was also no difference between secukinumab 300 mg and 150 mg in the overall rate of infections or in upper respiratory tract infections. In all indications, *Candida* infections were more frequent with secukinumab when compared to placebo and, in psoriasis trials, *Candida* infections were more common with the 300 mg dose compared to the 150 mg secukinumab regimen. The imbalance between the doses was limited to non-serious, localized mucosal or cutaneous candidiasis, with no reports of chronic or systemic disease in any treatment group. Across indications, *Candida* infections were responsive to standard treatment and did not necessitate discontinuation. No serious opportunistic infections were reported. No tuberculosis (TB) reactivation or viral hepatitis reactivation were observed in clinical trials, regardless of indication (psoriasis, PsA or AS).

Neutropenia was more frequently observed with secukinumab than with placebo, but most cases were mild, transient, and spontaneously reversible.

The incidence of hypersensitivity AEs was slightly higher with secukinumab compared with placebo, with the difference mostly due to mild to moderate urticaria and eczema not associated with systemic symptoms.

The incidence of selected rare events of interest (major adverse cardiovascular events and malignancies) adjusted for exposure over 52 weeks was comparable to placebo in clinical trials across multiple indications.

There was no clear association between treatment with secukinumab and new onset of inflammatory bowel disease but due to the potential involvement of the interleukin-17 (IL-17) pathway in the pathogenesis of the disease, it is not possible to rule out a potential increased risk of exacerbation.

Secukinumab 300 mg was comparable to 150 mg and both doses showed comparable safety to placebo and etanercept over 52 weeks of treatment.

Infections, neutropenia, and hypersensitivity are important identified risks, while malignancies, major adverse cardiovascular events, immunogenicity, Crohn's disease, and hepatitis B reactivation are important potential risks. Interaction with live vaccines is an important potential interaction (and also included as an important potential risk).

No new identified risks were reported. During the reporting interval, a Risk Management Plan (RMP) update was triggered upon request from Pharmacovigilance Risk Assessment Committee, to include suicidal ideation and behavior (SIB) as an important potential risk in the RMP on the basis that "although causality has not been established, SIB meets the criteria as important potential risk because a potential biological mechanism cannot be completely ruled out since the biological role of IL-17 receptor ligands is still largely unknown, and consideration of the potential public health impact". The RMP is currently being updated for this change. At its completion SIB will be listed as an important potential risk in the RMP.

No new safety signal was identified and no actions were taken for safety reasons during the reporting period of the latest drug safety update report.

The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance to the investigators, provided in the current version of the Investigator's Brochure (IB).

Taking into account the individual risks, the expected risk profile of secukinumab from a mechanism of action perspective in axSpA is anticipated to be similar to that of the approved indications.

From the standpoint of the overall risk benefit assessment, the current trial with secukinumab is justified.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in Section 5.2 (Exclusion criteria). If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

5 Population

The study population will consist of 300 randomized patients fulfilling the ASAS classification criteria for axSpA with active disease (measured by ASDAS ≥ 2.1 and elevated CRP and/or active inflammation on MRI of the sacroiliac joints and/ or spine) inadequately responding to or with intolerance/contraindications for NSAIDs, and with no previous treatment with a biological drug.

5.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must provide written, signed and dated informed consent before any study assessment is performed.
2. Male or non-pregnant, non-lactating female patients at least 18 years of age.
3. Diagnosis of axSpA (either r-axSpA (AS) or nr-axSpA) fulfilling the ASAS classification criteria for axSpA (Appendix 2).
4. Active disease as defined by having an ASDAS ≥ 2.1 at Screening and Baseline despite concurrent NSAID therapy, or intolerance/contraindication to NSAIDs.
5. Objective signs of inflammation at Screening as defined by:
   MRI of sacroiliac joints performed up to 3 months prior to screening showing acute inflammatory lesion(s),
   OR
   elevated quick CRP (> 5 mg/L),
   OR
   MRI showing acute inflammatory lesion(s) in the sacroiliac joints performed during screening period.
6. Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks (in total) in the past, with an inadequate response or failure to respond, or less if therapy had to be reduced due to intolerance, toxicity or contraindications.
7. Patients who are regularly taking NSAIDs (including cyclooxygenase-1 [COX-1] or cyclooxygenase-2 [COX-2] inhibitors) as part of their axSpA therapy are required to be on a stable dose for at least 1 week before randomization.
8. Patients taking MTX (7.5 mg/week to 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication but are required to be on a stable dose for at least 4 weeks before randomization.
9. Patients who are on a DMARD other than methotrexate (MTX) or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization.
10. Patients taking corticosteroids must be on a stable dose of ≤ 10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24.

5.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to Screening and evaluated by a qualified physician.
2. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
3. Patients who have previously been treated with TNFα inhibitors (investigational or approved).
4. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine).
5. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. CAMPATH, anti-CD3, anti-CD4, anti-CD5, anti-CD19).
6. History of hypersensitivity to secukinumab or adalimumab or their excipients or to drugs of similar chemical classes.
7. Contraindications for secukinumab or adalimumab.
8. Inability or unwillingness to undergo MRI (e.g. patients with pacemakers, aneurysm clips or metal fragments / foreign objects in the eyes, skin or body that are not MRI compatible) in case MRI is not already available (maximum 3 months old).
9. Use of any investigational agents within 4 weeks or within 5 half-lives of the drug (whichever is longer) prior to the Baseline Visit.
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
11. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in the European Union). Effective contraception methods include:
    - Total abstinence* (when this is in line with the preferred and usual lifestyle of the patient. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps).
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy

(failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device or intrauterine system.

* Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

12. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease or uveitis.
13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions, which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy.
14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥ 160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes.
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria:
    a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible laboratory error.
    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin.
16. History of renal trauma, glomerulonephritis, or patients with one kidney only, or a serum creatinine level exceeding 1.8 mg/dL (159.12 µmol/L).
17. Laboratory results at screening visit: total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1500/µL or hemoglobin < 8.3 g/dL (83 g/L).
18. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomization.
19. History of ongoing, chronic or recurrent infectious disease or evidence of TB infection as defined by a positive result is defined as an induration of ≥ 5 mm or according to local

practice/guidelines) or a positive QuantiFERON TB-Gold test. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If presence of latent TB is established, then treatment according to local country guidelines must have been initiated prior to randomization.

20. Patients positive for human immunodeficiency virus, hepatitis B or hepatitis C at randomization.
21. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
22. Live vaccinations within 6 weeks prior to Baseline or planned vaccination during study participation until 12 weeks after last study treatment administration.
23. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
24. Inability or unwillingness to undergo repeated venipuncture (e.g. because of poor tolerability or lack of access to veins).
25. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
26. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
27. History or evidence of ongoing alcohol or drug abuse, within the last 6 months before randomization.

6 Treatment

6.1 Study treatment

Investigational treatment – treat-to-target regimen

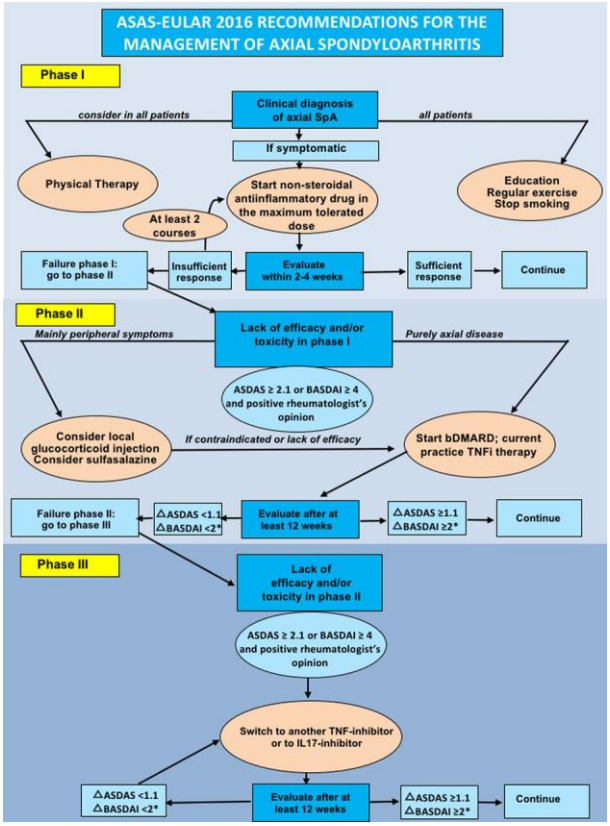
- **Secukinumab 150 mg**, liquid formulation in 1 mL prefilled syringe (PFS) for s.c. injection – all patients will receive 150 mg dose at Baseline, Week 1, 2, 3, 4 and 8. From Week 12, only responders (i.e. patients with ASDAS clinically important improvement, defined as change from Baseline ≥ 1.1) will continue to receive 4-weekly doses until Week 32 if they maintain the response.
- **Secukinumab 300 mg**, liquid formulation in 2 × 1 mL PFS for s.c. injection – patients who are non-responders at Week 12 will receive 4-weekly doses until Week 20. From Week 24, only responders will continue to receive 4-weekly doses until Week 32.
- **Secukinumab 300 mg as escape treatment,** liquid formulation in 2 × 1 mL PFS for s.c. injection - patients who were responders at Week 12, but experienced a loss of response (defined as ASDAS change from Baseline < 1.1) at Week 24 will receive 4-weekly 300 mg doses until Week 32.
- **Adalimumab biosimilar (Hyrimoz®) 40 mg**, liquid formulation in 0.8 mL PFS for s.c. injection – patients who are **non-responders to secukinumab 300 mg** at Week 24 will

receive from this time point biweekly doses of adalimumab biosimilar (Hyrimoz®) until Week 34.

Reference treatment – standard-of-care regimen

- Patients will receive treatment according to local practice standards by their treating physician following the current treatment recommendations. Current guideline recommends to start a biological disease modifying anti-rheumatic drug (bDMARD) after the failure of the NSAIDs therapy. According to the 2016 updated Ankylosing SpondyloArthritis International Society (ASAS)/European League Against Rheumatism recommendations, current practice is to start biological therapy with a TNFα blocker. After the failure of the first biologic therapy and in case of positive opinion of the rheumatologist, a switch to another TNFα-inhibitor or to IL-17-inhibitor should be considered (van der Heijde et al 2017). In accordance with these recommendation the treatment initiation, adjustment and switch will be conducted based on the disease activity and the positive opinion of the investigator. These therapy re-arrangement can be decided and performed at the time of regular study visit (e.g. Visit week 12 or Visit Week 24) or during unscheduled visits as per clinical routine of the investigator.

Figure 6-2 The 2016 updated Ankylosing SpondyloArthritis International Society (ASAS)/European League Against Rheumatism (van der Heijde et al 2017)



ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor; IL17-inhibitor, interleukin-17 inhibitor. *Either BASDAI or ASDAS, but the same outcome per patient.

Novartis will supply the investigational treatment in an open-label manner. Patients or caregivers will be instructed by site staff on how to self-administer the s.c. injection using the PFS containing the liquid formulation of secukinumab and/or adalimumab biosimilar (Hyrimoz®). Study treatment administrations at mandatory site visits (i.e. at Baseline, Week 12 and Week 24) will be performed by the patient under the supervision of site staff. Study treatment administrations outside of these site visits can either be performed at the patient's home or at optional study visits under the supervision of site staff as described in Section 6.7.2. Patients receiving secukinumab will follow the secukinumab Instructions for Use (IFU) document, and patients receiving adalimumab biosimilar (Hyrimoz®) will follow the adalimumab biosimilar (Hyrimoz®) IFU document. The IFUs for the medication in the SOC arm will be provided by the investigator in accordance with her/his clinical routine. Site staff will administer the injection to patients who are not able or feel insecure to self-administer the PFS injection.

6.1.1 Additional study treatments

No additional treatment beyond investigational and reference treatment are included in this trial.

6.1.2 Treatment arms/group

Patients will be randomly assigned at the Baseline Visit to either the T2T group or the SOC group.

T2T group (n = 150)

Starting from the Baseline Visit, patients will be treated with secukinumab 150 mg s.c. weekly until Week 4 and then at Week 8.

At Week 12:

- If ASDAS clinically important improvement is achieved and maintained, patients will continue the treatment up to Week 32 if they maintain the response.
- If ASDAS clinically important improvement is not achieved, patients will receive escalated dose of secukinumab 300 mg s.c. every 4 weeks until Week 20.

At Week 24:

Patients who are receiving secukinumab 300 mg, and

- Achieved ASDAS clinically important improvement, will continue the treatment up to Week 32.
- Did not achieve ASDAS clinically important improvement, will be switched to adalimumab biosimilar (Hyrimoz®) 40 mg s.c. every 2 weeks until Week 34.

Escape arm

- Patients 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 experienced a loss of response, where loss of response is defined as ASDAS change from Baseline < 1.1.

SOC group (n = 150)

Patients will receive treatment according to local practice standards by their treating rheumatologist following the current treatment recommendations with NSAIDs as the first-choice drug treatment and DMARDs for patients with active disease despite the use (or intolerance/contraindication) of NSAIDs.

6.1.3 Treatment duration

Each patient will be treated for a maximum of 36 weeks (last dose of secukinumab at Week 32, last dose of adalimumab biosimilar (Hyrimoz®) at Week 34).

6.2 Other treatment

6.2.1 Concomitant therapy

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient is enrolled into the study. All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded on the appropriate case report form (CRF).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Methotrexate

Patients taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization.

Sulfasalazine

Patients taking sulfasalazine (≤ 3 g/day) must be on a stable dose for at least 4 weeks before randomization.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted if the dose was stable within the 2 weeks preceding randomization, up to a maximum daily dosage of 10 mg prednisone equivalent. Higher-dose, time-limited corticosteroid courses (bursts) may be permitted for exacerbations of medical conditions unrelated to axSpA (e.g. asthma, chronic obstructive pulmonary disease, contact dermatitis) after randomization.

Nonsteroidal anti-inflammatory drugs (including COX-1 or COX-2 inhibitors) and acetaminophen/paracetamol

Patients should have been on at least 2 different NSAIDs at the highest recommended dose for at least 4 weeks (in total) prior to randomization with an inadequate response or failure to respond, or less if therapy had to be withdrawn due to intolerance, toxicity or contraindications.

Patients regularly using NSAIDs, low strength opioids, or paracetamol/acetaminophen should be on a stable dose for at least 1 week before randomization to allow inclusion in the study.

6.2.2 Prohibited medication

6.2.2.1 Prohibited prior medication (washout periods)

Previous use of medication listed in Table 6-1 is either not allowed at all or the given medication must be washed out as indicated. Table 6-1 **refers to both treatment arms.**

Table 6-1 Prohibited prior treatments (both arms)

Prohibited prior treatments	Washout period before randomization
Biologic drugs directly targeting IL-17 or IL-17 receptor	Previous exposure at any time: exclusion criterion
TNFα inhibitors (e.g. adalimumab, infliximab, certolizumab, golimumab).	Previous exposure at any time: exclusion criterion
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g. alemtuzumab (Campath), anti-CD4, anti-CD]	Previous exposure at any time: exclusion criterion
Unstable dose of MTX or sulfasalazine	4 weeks
Other DMARD (incl. apremilast, except MTX and – in case of axSpA – sulfasalazine)	4 weeks
Leflunomide with cholestyramine washout	4 weeks
Unstable doses of NSAIDs (COX1 or COX2 inhibitors), low strength opioids, paracetamol/acetaminophen.	2 weeks
Analgesics, other than NSAIDs or paracetamol/acetaminophen or low strength opioids as described above	2 weeks
Systemic corticosteroids > 10 mg prednisone per day equivalent	2 weeks
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent per day	2 weeks
Any investigational treatment other than study medication or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Live vaccinations	6 weeks
Medical cannabis	2 weeks

axSpA=ankylosing spondyloarthritis, COX-1=cyclooxygenase 1, COX-2=cyclooxygenase 2, DMARD=disease modifying anti-rheumatic drug, IL-17=interleukin-17, MTX=methotrexate, NSAIDs=non-steroidal anti-inflammatory drugs

6.2.2.2 Prohibited concomitant medication (T2T arm only)

Use of the treatments displayed in Table 6-2 is NOT allowed after the start of the washout period (see Table 6-1) and **refers** to **T2T arm only**.

There is no prohibited concomitant treatment in SOC arm, all SOC patients should be treated at the discretion of the investigator and in accordance with current therapy recommendation.

Live vaccines should not be given until 12 weeks after the last study drug administration.

Table 6-2 Concomitant treatment in T2T arm

Prohibited treatments	Action to be taken
Biologic drugs directly targeting IL-17 or IL-17 receptor other than investigational drug	Discontinue study treatment
TNFα inhibitors (e.g. adalimumab, infliximab, certolizumab, golimumab) other than investigational drug	Discontinue study treatment
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g. alemtuzumab (Campath), anti-CD4, anti-CD	Discontinue study treatment
csDMARDs other than MTX or sulfasalazine	Protocol deviation
Leflunomide	Protocol deviation
High potency opioid analgesics (e.g. methadone, hydromorphone, morphine)	Protocol deviation
Analgesics (other than NSAIDs, paracetamol/acetaminophen or low strength opioids)	Protocol deviation
Any investigational treatment other than study medication or participation in any interventional trial	Discontinue study treatment
Systemic corticosteroids ≥ 10 mg prednisone equivalent per day Local (injectable) steroids: > 2 injections or >80 mg triamcinolone equivalent in total.	Dose increase should be avoided; dose reduction at the investigator's discretion
NSAIDs (including COX-1 and COX-2 inhibitors)	Dose increase should be avoided; dose reduction at the investigator's discretion
MTX or sulfasalazine	Dose increase should be avoided; dose reduction at the investigator's discretion
Live vaccinations	Discontinue study treatment
Medical cannabis	Protocol deviation

COX-1=cyclooxygenase 1, COX-2=cyclooxygenase 2, DMARD=disease modifying anti-rheumatic drug, IL-17=interleukin-17, MTX=methotrexate, NSAIDs=non-steroidal anti-inflammatory drugs, TNFα=tumor necrosis factor alpha

6.2.3 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a patient is experiencing either no benefit from participation in the study or worsening/exacerbation of his/her disease. Since patients in the SOC arm will receive treatment according to local practice standards by their treating rheumatologist the study protocol cannot dictate any rescue treatment. The Investigator decides if and which rescue treatment should be applied.

Although no T2T-arm-patient will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if treatment with prohibited biologics (as described in Section 6.2.2) is started, patients may remain in the study but must discontinue study treatment. Efficacy and safety will be assessed at each on-site study visit, and patients who are deemed by the investigator not to be benefiting from study treatment, or for any reason of the patient's own accord, will be free to discontinue study participation at any time.

Changes in NSAIDs, non-biologic DMARDs and corticosteroid concomitant therapy are permitted as per investigator's discretion. Use of rescue medication must be recorded on the corresponding CRF.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

Each patient is identified in the study by a Patient ID that is assigned when the patient is first enrolled for Screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient ID consists of the Center Number (Center No. as assigned by Novartis to the investigative site) with a sequential Patient No. suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available.

Patients can be re-screened (only once) - no study-related re-screening procedure should be performed prior to written re-consent by the patient. Once re-screened, the patient will be assigned with a new identifier. For these patients, the previous primary identifier will be collected in the eCRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Biometrics Department using a validated system that automates the random assignment of treatment groups to randomization numbers in the specified 1:1 ratio (T2T group, SOC group). The randomization scheme will be reviewed and locked after approval. According to the recommendations given in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 Guideline "Statistical Principles for Clinical Trials", the used block length is specified in a separate document which will be with-held from the study centers. The randomization list will be kept sealed in a secure location.

All study sites will be provided with a given set of sealed allocation cards.

At the Randomization Visit, the investigator will assign each patient who meets all the inclusion criteria and does not fulfill any of the exclusion criteria to the lowest available randomization number, open the corresponding treatment allocation card and treat the patient with the treatment noted on this card (i.e. T2T treatment or SOC treatment).

6.4 Treatment blinding

Not applicable.

6.5 Permitted dose adjustments and interruptions of study treatment

In the T2T arm study treatment dose adjustments are not permitted. Study treatment interruption is also not permitted with the following exception:

- Study treatment interruption is only permitted if, in the opinion of the investigator, a patient is deemed to be at a significant safety risk unless administration of investigational treatment is temporarily interrupted. In such cases study treatment should be interrupted

only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab or adalimumab biosimilar (Hyrimoz®) on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. The elimination of adalimumab may take up to 4 months (Humira® SmPC); in case a live vaccine has been administered due to a medical urgency, study treatment should be discontinued

Treatment and thus any dose adjustments and/or treatment interruption and/or permanent discontinuations in the SOC arm are at the discretion of the investigator.

Study treatment/reference treatment interruption or permanent discontinuation of study treatment/reference treatment will not affect the ability of the patient to remain in the study.

Any study treatment interruption must be recorded on the corresponding CRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All dates of study treatment and reference treatment administration will be recorded on the appropriate CRF.

Drugs administered prior to start of treatment and other drugs/procedures continued or started during the study treatment/reference treatment period will be entered in the appropriate CRF.

Compliance to study treatment and reference treatment is expected to be 100% if possible, unless temporary interruption is needed for safety reasons as described in Section 6.5. In case full compliance with the visit schedule for the T2T arm cannot be reached, visits and/or treatments that fall into the following tolerance levels do not constitute a PD:
V1 up to and including V4: +/- 2 days
V5: +/- 3 days
V6 up to and including V9: +/- 7 days
V10 up to and including V15 for patients treated with secukinumab: +/- 7 days
V10 up to and including V15 for patients treated with adalimumab: +/- 3 days

Compliance will be assessed continuously during the conduct of the study by Novartis study personnel using medication kits and corresponding documentation.

Study drug doses and corresponding dates of self-administration at home should be documented in a self-administration log. Patients are required to return the self-administration log as well as all dispensed study drug for a compliance check at their subsequent visit back to the study center. Compliance will be assessed by a field monitor using information provided by the patient and the authorized site personnel. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

For the T2T arm, each study site will be supplied with study drug in packaging as described under the investigational and reference treatment section (Section 6.1).

The investigator or site staff will allocate the treatment arm at the randomization visit as described in Section 6.3.2.

Treatment in the SOC arm is at discretion of the investigator – the medication will be prepared and dispensed as per the routine daily clinical practice of the investigator.

In the T2T arm, the investigator will follow the treatment scheme provided in Table 8-2 and dispense either one secukinumab 150 mg PFS, or 2 secukinumab 150 mg PFS or one adalimumab biosimilar (Hyrimoz®) 40 mg PFS per scheduled visit, depending on the time point and the patient's response at Week 12 and/or Week 24.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment for the T2T arm (secukinumab 150 mg, adalimumab biosimilar (Hyrimoz®) 40 mg) must be received by a designated person at the study site, handled and stored safely and properly and kept in a secure location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment and reference treatment

The T2T treatments (secukinumab 150 mg, and adalimumab biosimilar (Hyrimoz®) 40 mg) will be provided in PFSs for s.c. use. SOC treatments will be provided in accordance with

routine practice. Administration of the study treatments must occur after the study assessments for the visit have been completed. The PFS with the ready-to-use study treatment solution will be provided by the site staff to the patient. Detailed instructions on the self-administration of the T2T study treatment will be described in the IFUs for secukinumab and adalimumab biosimilar (Hyrimoz®) and provided to each patient.

The IFUs for the medication in the SOC arm will be provided by the investigator in accordance with her/his clinical routine.

During the scheduled study visits (Baseline, Week 12 and Week 24), T2T and SOC treatments will either be administered by the investigator/site staff or by the patient but under the supervision of the investigator/site staff.

At the Baseline Visit, patients or caregivers will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Patients will be asked to raise any questions and then to proceed with self-injection. However, if the patient is not comfortable self-injecting the study treatment, then the site staff or caregiver may administer it to the patient.

Study treatment administration outside mandatory study visits

At the Baseline Visit, patients will also decide if they would like to perform study treatment administrations that occur outside the mandatory study visits either at home or at optional study visits as included in the schedule of assessments (Table 8-1) and study treatment administration schedule (Table 8-2).

If the patient decides to attend the optional study visits, the patient will be required to self-administer the study treatment (via PFS) at the study site under the supervision of the site staff. If the patient opts for home administration, the patient will be required to self-administer the study treatment (via PFS) at home. If the patient is unable or unwilling to self-administer the treatment via PFS, a caregiver may administer the study treatment for him/her. Caregivers should be trained on the IFU prior to administering the study treatment to the patient.

Prior to self-administration at home, patients should contact the investigator/site staff in case they are experiencing any AE/SAEs, or have any concerns.

All dates of self-administrations by the patient during the study must be recorded on the appropriate CRF. Immediately before dispensing the package to the patient, site staff will note medication specifications on the source document (Drug Label Form) for that patient's unique Patient No.

The investigator must promote compliance by instructing the patient to take the treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment/reference treatment as prescribed.

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), institutional review board/independent ethics committee (IRB/IEC) approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document an ICF that complies with the ICH Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the patient.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments and indicates with an 'X', 'S', or 'C' the visits when they are performed. An 'X' designates assessments which need to be recorded in the source data and CRF by the investigator or site staff. 'S' designates assessments which are recorded in source documentation only. 'C' designates centrally analyzed laboratory or questionnaire results, which are entered into the database by a central laboratory or by data management; for these assessments, only the date of the assessment needs to be entered into the electronic case report form (eCRF) by the site staff. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue 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.

At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the CRF.

The timing of study treatment administration at home and at the study site for patients assigned to the T2T treatment group is additionally presented in Table 8-2.

Table 8-1 Assessment schedule

Visit Name/ Visit Number	**SV1**	**SV2**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**FUP**
Week	**-8 to-4**	**-4 to BSL**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**56**
Home administration visit, can be performed optionally at the site				yes	yes	yes	yes*	yes*		yes	yes		yes	yes	yes	yes	yes		
Safety monitoring visit for patients in T2T arm[1]							X	X											
Information and informed consent	X																		
Inclusion/exclusion criteria[2]	X	X	X																
Demography		X																	
axSpA classification and diagnosis (incl. peripheral involvement)		X																	
Upload of X-ray and/or MRI of sacroiliac joints[3]			C																
Relevant medical history/ current medical condition (incl. CV and EAM history)[2]	X	X	X																
Washout evaluation/ instruction	S																		
Smoking history		X																	
Prior/concomitant medication/non-drug therapy (incl. axSpA prior and concomitant medication)	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X	X[a]	X[a]	**X**	X[a]	X[a]	X[a]	X[a]	X[a]	X	X

Visit Name/ Visit Number	**SV1**	**SV2**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**FUP**
Week	**-8 to-4**	**-4 to BSL**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**56**
Physical examination		S	S						S			**S**						S	S
Vital signs		X	X						X			**X**						X	X
Height		X																	
Weight		X	X						X			**X**						X	
QuantiFERON TB-Gold test	C																		
Chest X-ray/MRI[4]		S																	
MRI sacroiliac joints and spine[5]	X																		
Upload of MRI sacroiliac joints and spine[6]			C																
HLA-B27[7]		C/X																	
[redacted]																			
Serum pregnancy test		C																	
Urine pregnancy test			S						S			**S**						S	S
AEs/SAEs (including injection site reactions)	X	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X	X[a]	X[a]	**X**	X[a]	X[a]	X[a]	X[a]	X[a]	X	X
Clinical laboratory standard variables (central laboratory)		C	C						C			**C**						C	C
HIV-, Hepatitis B- and Hepatitis C Screening	C																		
Additional laboratory assessments for patients in T2T arm (ESR, hsCRP, full blood count, ALT, Creatinine)							C	C											

Visit Name/ Visit Number	**SV1**	**SV2**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**FUP**
Week	**-8 to-4**	**-4 to BSL**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**56**
Urinalysis (dipstick)		S	S						S			**S**							S
Quick hsCRP (locally)	X	X	X						X			**X**							
hsCRP (central laboratory)		X	X						X			**X**							
ESR (locally)		X	X						X			**X**							
[redacted]																			
BASDAI[9]		C	C						C			**C**							
Patient's global assessment of disease activity[9]		C	C						C			**C**							
BASFI[9]			C						C			**C**							
BASMI			C						C			**C**							
Back pain (VAS)[9]			C						C			**C**							
ASAS health index[9]			C						C			**C**							
SF-36[9]			C						C			**C**							
ASQoL[9]			C						C			**C**							
FACIT-Fatigue[9]			C						C			**C**							
Physician's global assessment of disease activity			C						C			**C**							
ASDAS		X	X						X[10]			**X[10]**							
[redacted]																			

Visit Name/ Visit Number	**SV1**	**SV2**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**	**FUP**
Week	**-8 to-4**	**-4 to BSL**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**56**
[redacted]																			
Administration of T2T s.c. study treatment (see also Table 8-2)			X	X	X	X	X	X	X	X	X	**X**	X[11]	X	X[11]	X	X[11]		
SOC treatment at investigator's discretion			Documentation of SOC treatment in the eCRF																

AE=adverse event, ALT=Alanine Aminotransferase, ASAS= Ankylosing SpondyloArthritis International Society, ASDAS=ankylosing spondylitis disease activity score, ASQoL= ankylosing spondylitis quality of life, axSpA=axial spondyloarthritis, BASDAI= Bath ankylosing spondylitis disease activity index, BASFI=Bath ankylosing spondylitis functional index, BASMI=Bath ankylosing spondylitis metrology index, BSL=baseline, CV=cardiovascular, hsCRP=high sensitive C-reactive protein, EAM=extra-articular manifestations, eCRF=electronic case report form, ESR=erythrocyte sedimentation rate, FACIT-Fatigue=functional assessment of chronic illness therapy- fatigue, FUP=follow-up, HIV=human immunodeficiency virus, [redacted] MRI=magnetic resonance imaging, SAE=serious adverse event, SF-36=short form health survey, SOC=standard-of-care, SV1=screening visit 1, SV2=screening visit 2, TB=tuberculosis, T2T=treat-to-target, VAS=visual analog scale, CV=cardiovascular

Note: visits highlighted in grey are for patients who opt for administration of study treatment outside of mandatory visits at the study site instead of at home.*

*All patients in the T2T arm must visit the site at the obligatory safety monitoring visits (Visit 4 and Visit 5); however, secukinumab can be administered at home by the patient or a caregiver.

'X' designates assessments which need to be recorded in the source data and CRF by the investigator or site staff.

'S' designates assessments which are recorded in source documentation only.

'C' designates centrally analyzed laboratory or questionnaire results which are entered into the database by a central laboratory or by data management; for these assessments, only the date of the assessment needs to be entered into the eCRF by the site staff.

[a] only in case the patient has been seen for the optional visit at site, else, the information will be obtained at the next obligatory site visit.

[1] As according to the DGRh recommendation, for patients treated with secukinumab following laboratory parameters should be evaluated at the therapy week 4 and 8:m ESR, hsCRP, full blood count, ALT, Creatinine.

[2] Eligibility and relevant medical history assessments are conducted at SV1, SV2 and Baseline but recorded only once in the eCRF.

[3] The last available X-ray and/or MRI of the sacroiliac joints done in order to confirm/revise the axSpA diagnosis should be uploaded into the central reading platform.

[4] If patients do not have a chest X-ray available within 3 months of Screening, an X-ray should be performed after it is certain the patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. In some sites selected by Novartis, the X-ray assessment may be replaced by chest MRI assessment.

[5] MRIs performed up to 3 months prior to Screening will be accepted; MRI should be performed during Screening only if patient's quick CRP test is negative (i.e. ≤ 5 mg/L).

[6] In case an actual (not older than 3 months) MRI image of sacroiliac joints (and spine) is available, it should be uploaded into the central reading platform. If a patient has a negative quick CRP (i.e. ≤5 mg/L) at Screening, a MRI of the sacroiliac joints and spine must be performed during the Screening to ensure the presence of objective signs of inflammation of the sacroiliac joint and the MRI should be uploaded into the central reading platform.

[7] In case the patient has been already tested for HLA-B27 antigen, the result of the test will be entered in the eCRF and no central re-test will be performed.

[redacted]

[9] All questionnaires will be completed at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation.

[10] This will be recorded in the CRF for patients in T2T arm only; in case an objective estimation of ASDAS is not possible due to e.g. an increase of CRP caused by reasons other than axSpA-related inflammation (e.g. common cold), the escalation/switch of the T2T-treatment must be done at the discretion of the investigator, the re-estimation of the ASDAS must be performed at the unscheduled visit 2 weeks later.

[11] Adalimumab biosimilar (Hyrimoz®) only.

[redacted]

Table 8-2 Drug administration schedule for treat-to-target group

Visit **Week**	**Base line** **W0**	**Visit 1** **W1**	**Visit 2** **W2**	**Visit 3** **W3**	**Visit 4** **W4**	**Visit 5** **W8**	**Visit 6** **W12**	**Visit 7** **W16**	**Visit 8** **W20**	**Visit 9** **W24**	**Visit 10** **W26**	**Visit 11** **W28**	**Visit 12** **W30**	**Visit 13** **W32**	**Visit 14** **W34**
All patients*	S150	S150	S150	S150	S150	S150									
Responder at Week 12							S150	S150	S150	S150	n/a	S150	n/a	S150	n/a
Non-responder at Week 12**							S300	S300	S300						
Escape Treatment***										*S300*	n/a	*S300*	n/a	*S300*	n/a
Responder at Week 24										S300	n/a	S300	n/a	S300	n/a
Non-responder at Week 24										A40	A40	A40	A40	A40	A40

Visits highlighted in grey are home administration visits, which can also be performed optionally at the study site.

A40 = adalimumab biosimilar (Hyrimoz®) 40 mg s.c.; S150 = secukinumab 150 mg s.c.; S300 = secukinumab 300 mg s.c.; W = week, n/a = not applicable

* After evaluation of response at Week 12, the patient will either continue to be treated with secukinumab 150 mg until the end of study (see row responder at Week 12) or be escalated to secukinumab 300 mg s.c.; the response will be re-assessed at Week 24 prior to study drug administration (see row non-responder at Week 12).

** After evaluation of response at Week 24, the patient will either continue to be treated with secukinumab 300 mg until the end of study (see row responder at Week 24) or switched to adalimumab biosimilar (Hyrimoz®) 40 mg s.c. (see row non-responder at Week 24).

*** In case a Week 12 responder loses his/her response at Week 24, he/she should be treated with 300 mg secukinumab at Week 24, Week 28 and Week 32.

8.1 Screening

Screening will be flexible (up to 8 weeks in duration) in order to allow sufficient time for MRI of sacroiliac joints and spine. During Screening, the patient will be evaluated for eligibility in addition to all other assessments indicated in Table 8-1. Screening will consist of 2 consecutive visits. During Screening Visit 1, initial assessments will be performed as outlined in Table 8-1. At that visit, it will be determined whether MRI of sacroiliac joints and spine are required. Screening Visit 2 will be performed as follows:

- If the MRI assessment is ≤ 4 weeks prior to baseline, the investigator should proceed directly to Screening Visit 2 (SV2) on the same day and complete all assessments in the next 4 weeks prior to randomization.
- If the MRI assessment is more than 4 weeks prior to baseline, the patient should return for Screening Visit 2 at up to 4 weeks prior to baseline.

The rationale is that in all cases Screening Visit 2 must occur within the 4 weeks prior to randomization to ensure that the results of laboratory evaluations performed during the screening are still actual at baseline.
Screening Visit 1 and Visit 2 may be performed on the same day if possible.

8.1.1 Information to be collected on screening failures

Patients who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a Screen failure. The reason for Screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen failure patients. No other data will be entered into the clinical database for patients who are Screen failures, unless the patient experienced a SAE during the Screening phase (see Section 10.1.3 for reporting details).

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate CRF.

8.2 Patient demographics/other baseline characteristics

All Baseline assessments should be performed prior to first study drug administration. These may occur during the Screening period or at the Baseline Visit depending on the assessment (Table 8-1).

8.2.1 Demographic characteristics

Patient demographic data to be collected for all patients include: year of birth, sex, race, child-bearing potential (for females only), and source of patient referral.

8.2.2 Other baseline characteristics

8.2.2.1 AxSpA classification and diagnosis

Patient's disease history will be collected. The information to be collected and entered as "axSpA history" includes the following:

- Date of first signs and symptoms of axSpA including date of onset of inflammatory back pain
- r-axSpA (AS) diagnosis including X-ray with presence/absence of sacroiliitis or
- nr-axSpA diagnosis by MRI or by presence of human leukocyte antigen-B27 (HLA-B27)
- Positive spondyloarthritis (SpA) features (Appendix 2)

Diagnosis of axSpA (either r-axSpA (AS) or nr-axSpA) should have been in accordance with ASAS axSpA criteria (Appendix 2 and Appendix 3, Appendix 4) as defined in the inclusion criteria (Section 5.1). In addition, peripheral involvement will be recorded in the eCRF.

Central reading of images

The X-ray and/or MRI images with presence/absence of sacroiliitis performed for axSpA diagnosis confirmation or revision will be uploaded onto the platform of the central reading center by the site personnel. Only the last available image (X-ray and/or MRI) should be uploaded.

8.2.2.2 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions (other than axSpA) present prior to signing the ICF (including cardiovascular and extra-articular manifestations (EAM) history) will be recorded in the medical history CRF. Whenever possible, diagnoses and not symptoms will be recorded.

Significant findings that are observed after the patient has signed the ICF and that meet the definition of an AE must be recorded in the AE summary pages.

Cardiovascular comorbidities and extra-articular manifestations – medical history

Any information pertaining to cardiovascular medical history or EAMs, such as uveitis or inflammatory bowel disease, assessed prior to Screening should be reported as cardiovascular history/EAM in the eCRF. Cardiovascular risk factors should also be recorded.

8.2.2.3 Smoking history

The current and/or previous use of tobacco products will be recorded. Non-smokers will be advised not to start smoking during the study.

8.2.2.4 Prior medication/concomitant medication

All previous and current axSpA treatment other than study drugs will be captured as documented in the patient's medical history or reported by the patient or determined by the investigator at the Screening Visit and documented in the eCRF.

All other prior medications taken within the 6 months preceding the study Screening Visit (Visit 1), any other relevant medication taken before these 6 months at the discretion of the investigator, and any concomitant medication irrespective of the start date will be captured in the eCRF.

8.2.2.5 Height

Height in centimeters (cm) will be measured without shoes.

8.2.2.6 Tuberculosis screening

A central laboratory test (QuantiFERON TB-Plus test) be performed at the Screening Visit to screen the patient population for latent TB infection. The results must be known prior to randomization to determine the patient's eligibility for the study.

Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that

- The patient has no evidence of active TB
- If presence of latent TB is established then treatment according to local country guidelines must have been initiated.

Central laboratory test for tuberculosis screening

The test (e.g. QuantiFERON TB-Plus test) will be analyzed by the central laboratory. Details on the collection, processing, and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

8.2.2.7 X-ray or MRI of the chest

A chest X-ray (posteroanterior view) or MRI at Screening (or within 3 months prior to Screening) will be performed to rule out the presence of a pulmonary malignancy or infectious process, in particular, TB. The results must be known prior to randomization to determine the patient's eligibility for the study. These assessments will be documented in source records only and will not be entered into the CRF.

8.2.2.8 MRI of the sacroiliac joints and spine

An actual MRI image (not older than 3 months) of the sacroiliac joints and spine will be accepted. In case patient's quick CRP is negative at Screening, a MRI of the sacroiliac joints and spine will be performed during Screening. The MRI will include T1 and short TI inversion recovery sequences of the sagittal spine (cervical, thoracic, and lumbar) and oblique coronal of the pelvis including both sacroiliac joints.

[redacted]

8.2.2.9 HLA-B27

A blood sample to analyze HLA-B27 will be obtained at SV2 from all patients for whom the antigen has not been determined in the past.

Details on the collection, handling and shipment of the sample to the central laboratory will be provided to investigators in the laboratory manual.

8.2.2.10 Other baseline assessments

Other Baseline characteristic data to be collected for all patients at either the Screening or Baseline Visit (see also Table 8-1) include the following:

- Physical examination, body weight, vital signs, clinical laboratory assessments as described in Section 8.4 and AEs/SAEs (including injection site reactions) as described in Section 10.
- For women of childbearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at Baseline as described in Section 8.4.5.
- Baseline assessments of ASDAS, BASDAI, erythrocyte sedimentation rate (ESR), hsCRP /quick hsCRP, [redacted] as described in Section 8.3.
- Documentation of SOC treatment in the eCRF.

Whenever possible, diagnoses and not symptoms will be recorded.

8.3 Efficacy

- Ankylosing spondylitis disease activity score (ASDAS)
- Bath ankylosing spondylitis disease activity index (BASDAI)
- Patient's global assessment of disease activity (visual analog scale [VAS])
- Physician's global assessment of disease activity (VAS)
- Bath ankylosing spondylitis functional index (BASFI)
- Bath ankylosing spondylitis metrology index (BASMI)
- Patient's assessment of back pain intensity (VAS)
- [redacted]
- [redacted]

All efficacy assessments should be performed prior to administration of study treatment/reference treatment.

8.3.1 Assessment of SpondyloArthritis International Society response criteria (ASAS)

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

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. CRP (acute phase reactant)

ASAS assessment will be performed only during the analysis, will not be collected on the eCRF during the study, only ASAS compounds as listed above will be collected in the eCRF as indicated in the table 8-1.

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 at all in the remaining domain.

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.

8.3.1.1 Patient's global assessment of disease activity (VAS)

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?*".

8.3.1.2 Patient's assessment of 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?*".

8.3.1.3 Bath ankylosing spondylitis functional index

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 patients' 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.

8.3.1.4 Bath ankylosing spondylitis disease activity index

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 2 scores relating to morning stiffness is taken. The mean of questions 5 and 6 is added to the scores from questions 1 to 4. 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 patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical studies evaluating new drug therapies directed at AS. The BASDAI is a quick and simple index taking between 30 seconds and 2 minutes to complete.

See Appendix 5 for further details.

8.3.1.5 Bath ankylosing spondylitis metrology index

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

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

Additionally, the following assessments should be taken:

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

See Appendix 6 for further details.

8.3.1.6 Erythrocyte sedimentation rate

Blood for ESR, which is helpful in diagnosing inflammatory diseases, will be used to monitor disease activity and response to therapy. ESR assessments will be performed locally at the study centers, using a centrally provided assessment kit.

8.3.1.7 High sensitive Quick C-reactive protein test/ high sensitive C-reactive protein test

This assessment will be performed in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. The quick hsCRP assessments will be performed locally at the study centers using a centrally provided assessment kit. The result of the quick hsCRP will be used to confirm eligibility of the patient (ASDAS ≥ 2.1 or CRP > 5 mg/L) at Screening and Baseline or to estimate further treatment of patients in the T2T arm at the Week 12 or Week 24 visit. In addition, the hsCRP assessment will be performed centrally as indicated in Table 8-1 and used in final data analyses only.

8.3.2 Ankylosing spondylitis disease activity score

The ASDAS is a composite index to assess disease activity in AS (Lukas et al 2009, Sieper et al 2009, Machado et al 2011, Machado et al 2018). The ASDAS-ESR and ASDAS-CRP will be utilized to assess the disease activity status. Parameters used for the ASDAS include spinal pain (BASDAI question 2), the patient's global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and CRP in mg/L (or ESR).

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).

ASDAS 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 can be considered to be enrolled into the study.

In addition, for patients in T2T arm the ASDAS will be calculated via eCRF at week 12 and week 24 in order to estimate the response and to decide further treatment.

8.3.3 Physician's global assessment of disease activity

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." To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity when performing his own assessment on that patient.

[redacted]

[redacted]

8.3.6 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across all r-axSpA (AS) and nr-axSpA trials studies.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to the AE section (Section 10).

8.4.1 Physical examination

The physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to the ICF must be included in the relevant medical history CRF. Significant findings made during a physical exam after signing the ICF which meet the definition of an AE must be recorded on the appropriate CRF, capturing AEs and if SAE criteria are met, also as a SAE.

8.4.2 Body weight

Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing) will be measured without shoes.

8.4.3 Vital signs

Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in a sitting position.

If possible, vital sign assessments should be performed by the same study site staff member using the same validated device throughout the study.

8.4.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. Clinically notable laboratory findings are defined in Appendix 1. All patients with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

8.4.4.1 Hematology

Hemoglobin, hematocrit, platelet count, red blood cell, WBC and differential WBC counts will be measured at scheduled visits.

8.4.4.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST, ALT, gamma-glutamyltransferase (GGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

8.4.4.3 Lipid panel

A lipid profile including high density lipoprotein, low density lipoprotein, cholesterol and triglycerides..

8.4.4.4 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page. In case any abnormality are observed in the result of the dipstick, a urine sample will be send to central laboratory for further examination.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the Screening Visit, and local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing may be performed if requested by local requirements.

Secukinumab and adalimumab biosimilar (Hyrimoz®) should not be given to pregnant women; therefore effective methods of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 4.2).

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy.
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, follicle-stimulating hormone testing is required of any female patient, regardless of reported reproductive/menopausal status at Screening/Baseline.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

8.5 Additional assessments

8.5.1 Health-related quality of life outcomes

The impact of axSpA on various aspects of patient's health-related quality of life (QoL) will be assessed by the following instruments:

- SF-36 version 2 (acute form)
- Ankylosing spondylitis quality of life (ASQoL)

- ASAS health index (ASAS-HI)
- FACIT-Fatigue

All questionnaires will be available in the local languages of the participating countries.

All questionnaires will be completed at the scheduled study visit prior to the patient seeing the investigator for any clinical assessment or evaluation.

All patients will complete the patient reported outcome (PRO) questions on paper. Patients should be given sufficient instruction, space, time and privacy to complete all study PROs. The study coordinator should check the responses to the questionnaire for completeness and encourage the patient to complete any missing responses. Attempts should be made to collect responses to all PROs for all patients, including from those who prematurely discontinue prior to the study evaluation completion visit, however, if patients refuse to complete PROs, this should be documented in study source records. Patient's refusal to complete study PROs are not protocol deviations.

Guidelines for administering the PRO questionnaires can be found in Appendix 7. A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 10.1 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

8.5.1.1 Medical outcome short form health survey (SF-36) version 2 acute form

The SF-36 is a widely used and extensively studied instrument to measure health-related QoL among healthy patients and patients with acute and chronic conditions. It consists of eight subscales 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 and the Mental Component Summary also can be computed (McHorney et al 1993). 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 purpose of the SF-36 in this study is to assess the health-related QoL of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

8.5.1.2 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.

8.5.1.3 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 ICF Core Set, as presented in Table 8-3. 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. In addition, the Environmental Factor (EF) Item Set (Appendix 10) 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 2016).

Table 8-3 Items of the ASAS health index

Item	Categories	ICF number
Pain sometimes disrupts my normal activities.	Pain	b280
I find it hard to stand for long.	Maintaining a body position	d415
I have problems running.	Moving around	d455
I have problems using toilet facilities.	Toileting	d530
I am often exhausted.	Energy and drive	b130
I am less motivated to do anything that requires physical effort.	Motivation	b1301
I have lost interest in sex.	Sexual functions	b640
I have difficulty operating the pedals in my car.	Driving	d475
I am finding it hard to make contact with people.	Community life	d910
I am not able to walk outdoors on flat ground.	Moving around	d455
I find it hard to concentrate.	Handling stress	d240
I am restricted in traveling because of my mobility.	Recreation and leisure	d920
I often get frustrated.	Emotional functions	b152
I find it difficult to wash my hair.	Washing oneself	d510
I have experienced financial changes because of my rheumatic disease.	Economic self-sufficiency	d870
I sleep badly at night	Sleep	b134
I cannot overcome my difficulties.	Handling stress	d240

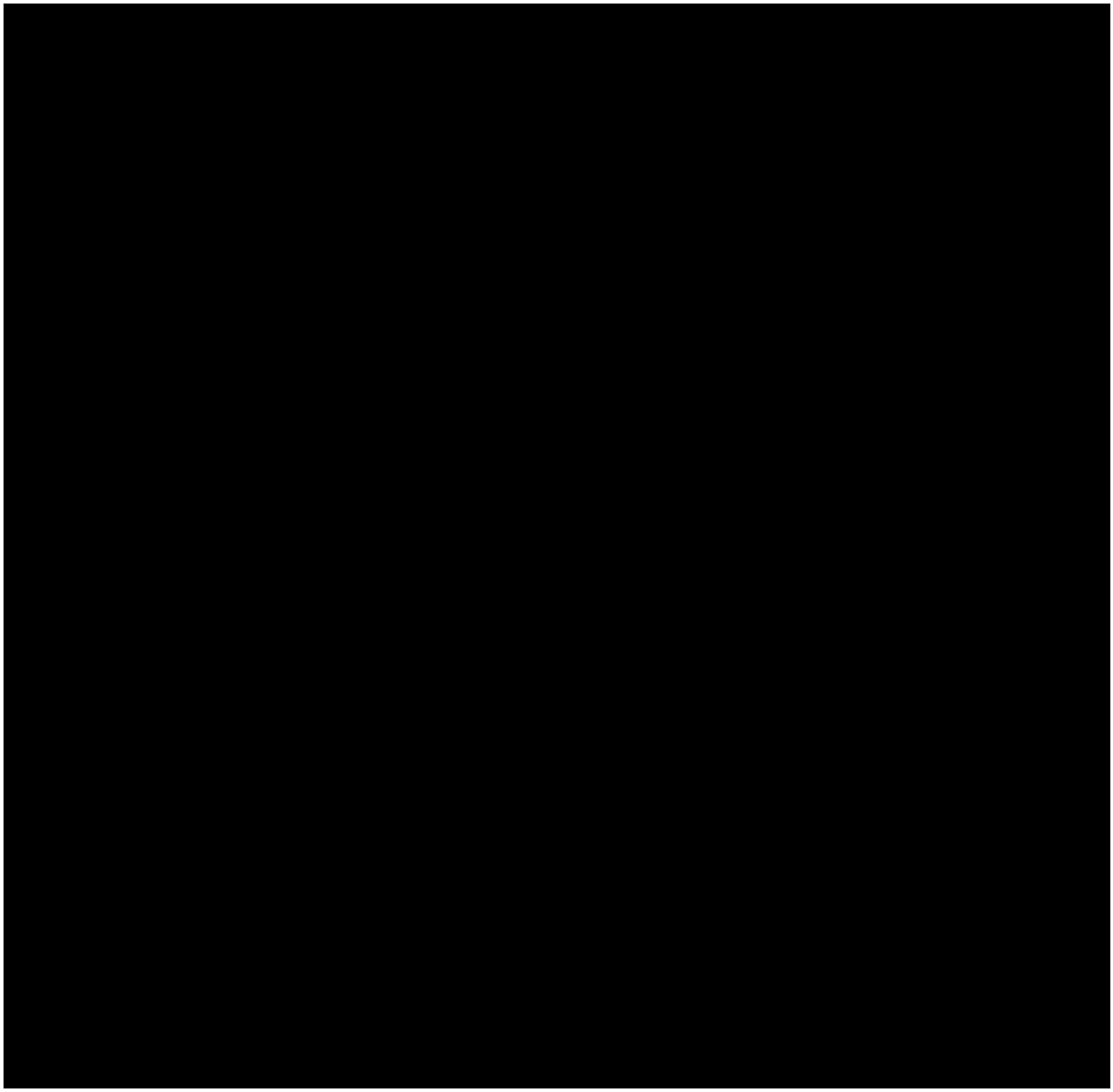
Item	Categories	ICF number

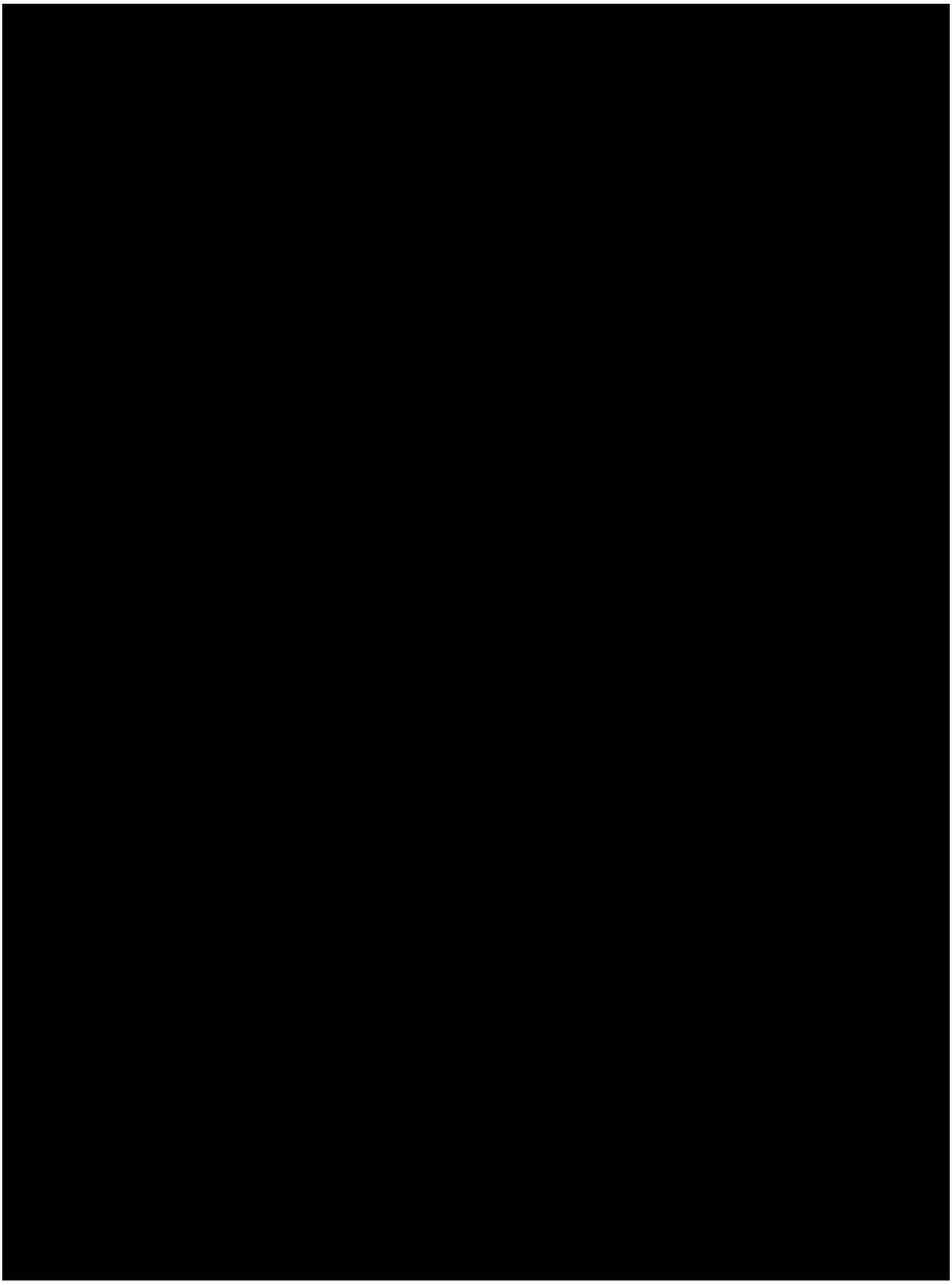
ICF = International Classification of Functioning, Disability and Health

Source: Kiltz et al 2014

8.5.1.4 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.





9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment / reference treatment

Discontinuation of study treatment/reference treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a patient. The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent
- Emergence of the following adverse events:

a. Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with prohibited comedication

b. Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or noninvasive malignant colon polyps which are being or have been removed

c. Life-threatening infection

d. Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the patient at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1.)

e. Pregnancy

g. Any protocol deviation that results in a significant risk to the patient's safety

- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Unsatisfactory therapeutic effect

If discontinuation of study treatment/reference treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the patient's premature discontinuation of study treatment and record this information.

Patients who discontinue study treatment/reference treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

After study treatment/reference treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New/concomitant treatments
- AEs/SAEs

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment/reference treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol i.e. Follow-up Visit /Week 56 (see Table 8-1). Information on the patient's completion or discontinuation from the study and the reason for discontinuation from the study will be recorded on the appropriate Study Phase Completion page in the eCRF.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. Based on the individual risk/benefit profile of a patient, treatment options may include DMARDs.

In case of follow-up medical care with a biologic treatment the waiting period before initiating treatment will be at the discretion of the investigator or a minimum of 5-half-lives of the selected biologic treatment, whichever is longer.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. In addition, all reports of intentional misuse and abuse of the study treatment are also considered an AE irrespective if a clinical event has occurred. See Section 10.1.5 for an overview of the reporting requirements.

The investigator has the responsibility for managing the safety of individual patient and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Adverse events must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.3):

1. The severity grade:
   - Mild: Usually transient in nature and generally not interfering with normal activities
   - Moderate: Sufficiently discomforting to interfere with normal activities
   - Severe: Prevents normal activities
2. Its relationship to the investigational treatment and other treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient.
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.3 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding investigational treatment and other treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed

- Dose reduced/increased
- Drug interrupted/withdrawn.

6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Conditions that were already present at the time of informed consent should be recorded in the patient's medical history.

Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 20 weeks (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an IN or an aggregate safety finding. New information might require an update to the informed consent and has then to be discussed with the patient.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in patients with the underlying disease. Clinically notable laboratory values are presented in Appendix 1.

10.1.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- Fatal
- Life-threatening.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction, it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline)

- Results in persistent or significant disability/incapacity.

- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes above.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the products are also considered SAEs irrespective if a clinical event has occurred.

10.1.3 SAE reporting

Randomized patients

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent until 20 weeks after the patient has discontinued or stopped study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen failures

SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at

a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form (this may be a paper or electronic SAE CRF); all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the period of 20 weeks after last administration of study drug should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety. Pregnancy follow-up (Birth, 1, 3 and 12 months after the expected delivery) should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

Additionally, pregnancy outcomes (Birth, 1, 3 and 12 months after the expected delivery) should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate eCRF, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in approximately 13000 patients and healthy patients exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17a on the liver. Standard liver function tests will be obtained at regular intervals, but special measures for liver safety monitoring are not planned. For further information on standard liver function tests, see Appendix 1.

10.2.2 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in approximately 13000 patients and healthy patients exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17a on the kidney. All patients with laboratory tests containing clinically significant abnormal values (see Appendix 1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function

tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data collection and database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

Designated investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated contract research organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study treatment(s) and reference treatment dispensed to the patient and all dosage changes will be entered into the eCRF.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis/sponsor employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis/sponsor clinical teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original ICF signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis/sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

12 Data analysis and statistical methods

The data will be analyzed by Novartis and/or a designated CRO.

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

The primary analyses for all efficacy and safety endpoints will be carried out after the last patient completed Week 24 assessment. [redacted]

12.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized Analysis Set (RAS): The RAS is defined as all patients who were randomized. Unless otherwise specified, miss-randomized patients will be excluded from the RAS.

Full Analysis Set (FAS): The FAS comprises all patients to whom study treatment/reference treatment has been assigned by randomization. According to the intent to treat principle,

patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Safety Set: The Safety Set includes all patients who received at least one dose of study treatment/reference treatment. Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.2 Patient demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively by treatment group and in total for the FAS and Safety Set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at Baseline will be summarized by system organ class and preferred term (PT), and by treatment group.

12.3 Treatments

The Safety Set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure to study treatment by treatment group will be summarized by means of descriptive statistics using the Safety Set. In addition, the number of patients with exposure of certain thresholds will be displayed. Compliance will be calculated based on documented study drug administrations and syringe counts and displayed by treatment group and study phase.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system, by treatment group. Prior treatments are defined as treatments taken and stopped prior to first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last day of study visit will be a concomitant treatment, including those which were started pre-Baseline and continued into the treatment period. Treatments will be presented in alphabetical order, by ATC codes and grouped by anatomical main group. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC.

12.4 Analysis of the primary efficacy endpoint

12.4.1 Definition of primary endpoint

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

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

The analysis of the primary variable will be based on the following:

- Analysis set: FAS
- Variable of interest: proportion of patients achieving treatment response as defined by the ASAS40 criteria at Week 24.
- Intervention effect: effect between a secukinumab T2T dose escalation regime vs. a SOC treatment approach based upon investigator's discretion regardless of adherence to randomized treatment.
- Summary measure: Odds ratio (OR)

12.4.2 Statistical model, hypothesis, 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 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 OR, the corresponding 95% confidence interval (CI) and the p-value will be given. The H0 of equal odds will be rejected if the 2-sided p-value from the logistic regression model for the factor "treatment" is < 0.05. The primary efficacy analysis will be based on the FAS. The primary analysis will be performed when all patients have completed the Week 24 assessment.

12.4.3 Handling of missing values/censoring/discontinuations

Patients will be analyzed irrespective of adherence to assigned treatment regimen. Patients without a valid ASAS40 assessment at Week 24 will be regarded as non-responders for the primary analysis. Non-responder imputation will also be applied to all secondary response variables.

12.4.4 Sensitivity and supportive analyses

Sensitivity analyses

Sensitivity analyses as well as supportive analyses will be conducted in order to provide evidence that the results seen from the primary model results are robust. These analyses will center on the deviations in model assumptions and the treatment of missing data.

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

Supportive analyses

Possible effect modification due to patient characteristics will be explored by subgroup analyses for sex, age class, disease severity and CRP blood level at Baseline. The primary model may also be recalculated with these factors included as well as with the respective terms for a subgroup*treatment interaction.

12.5 Analysis of secondary [redacted] endpoints

The primary analysis will be performed when all patients have completed the Week 24 assessment.

12.5.1 Analysis of secondary [redacted] efficacy endpoints

ASAS20/40 response

ASAS20/ ASAS40 response at Week 12, Week 24 [redacted] will be evaluated using the multiple logistic regression model utilized for the primary efficacy variable.

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.

AS disease activity score

The proportion of patients meeting the ASDAS definition of inactive disease (< 1.3), ASDAS clinically important improvement (change in ASDAS ≥ 1.1) and ASDAS major improvement (change in ASDAS ≥ 2.0) as well as 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 between-treatment difference in change from Baseline in ASDAS will be evaluated using a mixed-effect model repeated measures (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.

Bath ankylosing spondylitis disease activity index

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

Furthermore, the between-treatment difference in change from Baseline in BASDAI will be 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.

Bath ankylosing spondylitis functional index

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.

Bath ankylosing spondylitis metrology index and chest expansion

The between-treatment difference in change from Baseline in BASMI 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.

Change in patient's global assessment of disease activity

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.

Change in ASDAS-CRP and ESR

The between-treatment difference in change from Baseline in ASDAS-CRP and ASDAS-ESR will be evaluated using a MMRM. Treatment group and analysis visit as factors and Baseline ASDAS and weight as continuous covariates will be included in the model. Treatment group by analysis visit and Baseline ASDAS 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]

[redacted]

[redacted]

12.5.2 Analysis of secondary safety endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) will include only data from the on-treatment period with the exception of Baseline data, which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (i.e. treatment-emergent AEs as defined below).

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.

Adverse events

All information obtained on AEs will be displayed by treatment group and patient.

The number (and percentage) of patients with treatment-emergent AEs (defined as events started after the first dose of study medication 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.
- By treatment, standardized MedDRA query and PT.

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs leading to discontinuation, AEs leading to dose adjustment and AE of special interest.

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. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

Vital signs

All vital signs data will be listed by treatment group, patient, and visit/time, and if ranges are available, abnormalities will be flagged. 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 patients with both Baseline and post-Baseline values.

12.5.3 Analysis of secondary [redacted] health-related quality of life endpoints

Health-related quality of life assessments will be evaluated based on the FAS unless otherwise specified.

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

For the change in SF-36 summary scores (PCS and MCS), between-treatment differences will be evaluated utilizing a MMRM. 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 and MCS 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.

Ankylosing spondylitis quality of life

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.

Functional assessment of chronic illness therapy – fatigue

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.

ASAS health index

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.

12.7 Sample size calculation

12.7.1 Primary endpoint

The sample size was calculated based on the primary efficacy variable ASAS40 response at Week 24 for the Full Analysis Set. 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 patients, 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 patients did not achieve an ASDAS clinically important improvement (defined as change from BL of $\geq$ 1.1) criterion at Week 12. Taking into account the longer duration of active treatment with secukinumab 150 mg and the substantial proportion of patients 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 patients 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 patients (150 patients in the T2T and 150 patients in the SOC arm) should be randomized into this study.

An IA will be conducted to evaluate and possibly adapt the sample size calculated in order to show superiority in the primary efficacy endpoint.

Through an IA sample size adaption would be possible in case the assumed number of patients is not enough or is too high. Results from a sample size simulation using the above mentioned response values as well as the parameters for the two-stage adaptive design resulted in the assumption of a maximum of 400 patients spanning over the two study stages.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis/sponsor systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures, and are performed according to written Novartis/sponsor processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for patient safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

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

Clinically notable values will be forwarded to Novartis/CRO at the same time that they are sent to investigators. Any action based on these laboratory values should be discussed with Novartis/CRO personnel.

Table 16-1 Safety analyses: expanded limits and notable criteria

	Final Harmonization	
Laboratory Variable	**Notable Criteria**	
	Standard Units	**SI Units**
LIVER FUNCTION AND RELATED VARIABLES		
SGOT (AST)	> 3 x ULN	> 3 x ULN
SGPT (ALT)	> 3 x ULN	> 3 x ULN
GGT		
Bilirubin	> 2 x ULN	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN	> 2.5 x ULN
RENAL FUNCTION, METABOLIC AND ELECTROLYTE VARIABLES		
Creatinine (serum)	> 2 x ULN	> 2 x ULN

16.2 Appendix 2: Assessment of spondyloarthritis international society criteria for axial spondyloarthritis

ASAS criteria for classification of axSpA will be applied as defined by Sieper et al (2009).

Diagnosis of axial spondyloarthritis according to the assessment of spondyloarthritis international society classification criteria

Diagnosis of axSpA (either AS or nr-axSpA) according to ASAS axSpA classification criteria to be applied in patients with back pain for at least 3 months and age of onset < 45 years:

- Sacroiliitis on imaging with ≥ 1 SpA feature **or**
- HLA-B27 positive with ≥ 2 SpA features

Sacroiliitis on imaging

- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA (see Appendix 6)
- Definite radiographic sacroiliitis according to the modified New York diagnostic criteria (van der Linden et al 1984) (see Appendix 5)

Spondyloarthritis features

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease or colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated CRP

Source: Sieper J, Rudwaleit M, Baraliakos X, et al (2009) The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis.; 68 Suppl 2:ii1-44

16.3 Appendix 3: Modified New York diagnostic criteria for ankylosing spondylitis

Patients with axSpA are classified as having AS, based on the fulfillment of the 1984 modified New York diagnostic criteria (van der Linden et al 1984).

Clinical criteria for ankylosing spondylitis

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

Radiological criterion for ankylosing spondylitis

- Sacroiliitis grade ≥ 2 bilaterally or grade 3–4 unilaterally

Definite AS if the radiological criterion is associated with at least one clinical criterion.

Source: van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of the diagnostic criteria for ankylosing spondylitis - A proposal for modification of the New York criteria. Arthritis Rheum; 27:361-8.

16.4 Appendix 4: Definition of sacroiliitis on imaging

Sacroiliitis on magnetic resonance imaging

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 edema/osteitis highly suggestive of sacroiliitis is mandatory
- The presence of synovitis, capsulitis, or enthesitis only without concomitant subchondral bone marrow edema/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

Sacroiliitis on X-ray

Grading of radiographic sacroiliitis according to the New York diagnostic criteria (Bennett and Burch 1968):

- Grade 0: normal
- Grade 1: suspicious changes
- Grade 2: minimal abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width)
- Grade 3: unequivocal abnormality - (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis
- Grade 4: severe abnormality (total ankylosis)

Sources:

Bennett and Burch (1968) The epidemiological diagnosis of ankylosing spondylitis. Book: Population studies of rheumatic diseaseas, pp. 305-313

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16.5 Appendix 5: Bath Ankylosing Spondylitis Disease Activity Index

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. How would you describe the overall level of **fatigue/tiredness** you have experienced?
2. How would you describe the overall level of AS **neck, back or hip pain** you have had?
3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?
4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**
6. How long does your morning stiffness last from the time you wake up?

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The mean of questions 5 and 6 is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. 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 Ankylosing Spondylitis. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete).

16.6 Appendix 6: Bath Ankylosing Spondylitis Metrology Index

Cervical rotation

Cervical rotation is measured twice with the subject supine on plinth, head in neutral position, forehead horizontal (if necessary, with the head on a pillow or foam block, which must be documented for future reassessments). A goniometer (preferably a gravity goniometer) is placed centrally on the forehead. Subject rotates head as far as possible to the right, keeping shoulders still; ensure no neck flexion or side flexion occurs. The angle between the sagittal plane and the new plane after rotation is recorded. The higher reading of two assessments is recorded in degrees. The same procedure is repeated twice for the left side. Record the mean of the higher reading from the right side and the higher reading from the left side.

Tragus to wall distance

Tragus to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level and the subject takes maximal effort to touch the head against the wall. The distance between the tragus and the wall is assessed on each side, and an average of the two distances from each side is calculated. The procedure is repeated, and the shorter of the two average assessments is reported.

Spinal lateral flexion (lumbar lateral flexion)

Subject stands with heels and buttocks touching the wall, knees straight, shoulders back, and hands by the side. The subject bends to the right side as far as possible, without lifting the left foot/heel or flexing the right knee and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when subject bends to the side is subtracted from the distance when subject stands upright. The higher of two tries is recorded. The maneuver is repeated on the left side. Record the mean of the larger difference from the right side and the larger difference from the left side.

Lumbar flexion (modified Schoeber index)

Subject is standing erect. Set marks in upright position 5 cm below and 10 cm above lumbosacral junction (spinal section of a line joining the dimples of Venus). Measure the difference between the distance between marks in a standing position (15 cm) vs. a forward flexed position when the subject bends forward as far as possible, keeping the knees straight. The procedure is repeated, and the higher difference of the two tries is reported.

Maximal intermalleolar distance

Subject is lying down with the legs separated as far as possible with knees straight and toes pointing upwards. Alternatively, the subject stands and separates the legs as far as possible. Distance between medial malleoli is measured, and the higher of the two readings is recorded.

Chest expansion

Chest expansion is measured with the subject's hands resting on or behind the head. The measurement is taken at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in cm (to the nearest 0.1 cm) is recorded twice, and the higher difference of the two tries is reported.

Occiput-to-wall distance

Occiput to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level, and the subject takes maximal effort to touch the head against the wall. The distance between the occiput and the wall is assessed, and the shorter of the two readings is reported.

16.7 Appendix 7: Guidelines for administering the questionnaires for patient reported outcomes

Before study start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the study and identify any items where a patient's response might highlight issues of potential concern.

For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a patient responds 'most or all of the time', then the study coordinator should inform the study investigator.

Before completion

1. Subjects should be provided with the correct questionnaire at the appropriate visits and in the appropriate language
2. Subjects should have adequate space and time to complete the forms
3. Questionnaire should be administered before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response
2. Only one response for each question
3. Also see "Addressing Problems and Concerns"

After completion

1. Check for completeness and not for content*
2. Check for multiple responses that were made in error

*However, any response which may directly impact or reflect the patient's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator).

Addressing problems and concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The patient does not want to complete the questionnaire(s)

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of patients. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline and thank the patient.

The patient is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The patient wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the patient provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for patient self-report. Patients should be discouraged from asking a family member or friend for help in completing a questionnaire.

The patient does not want to finish completing the questionnaire(s)

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the patient.

The patient is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

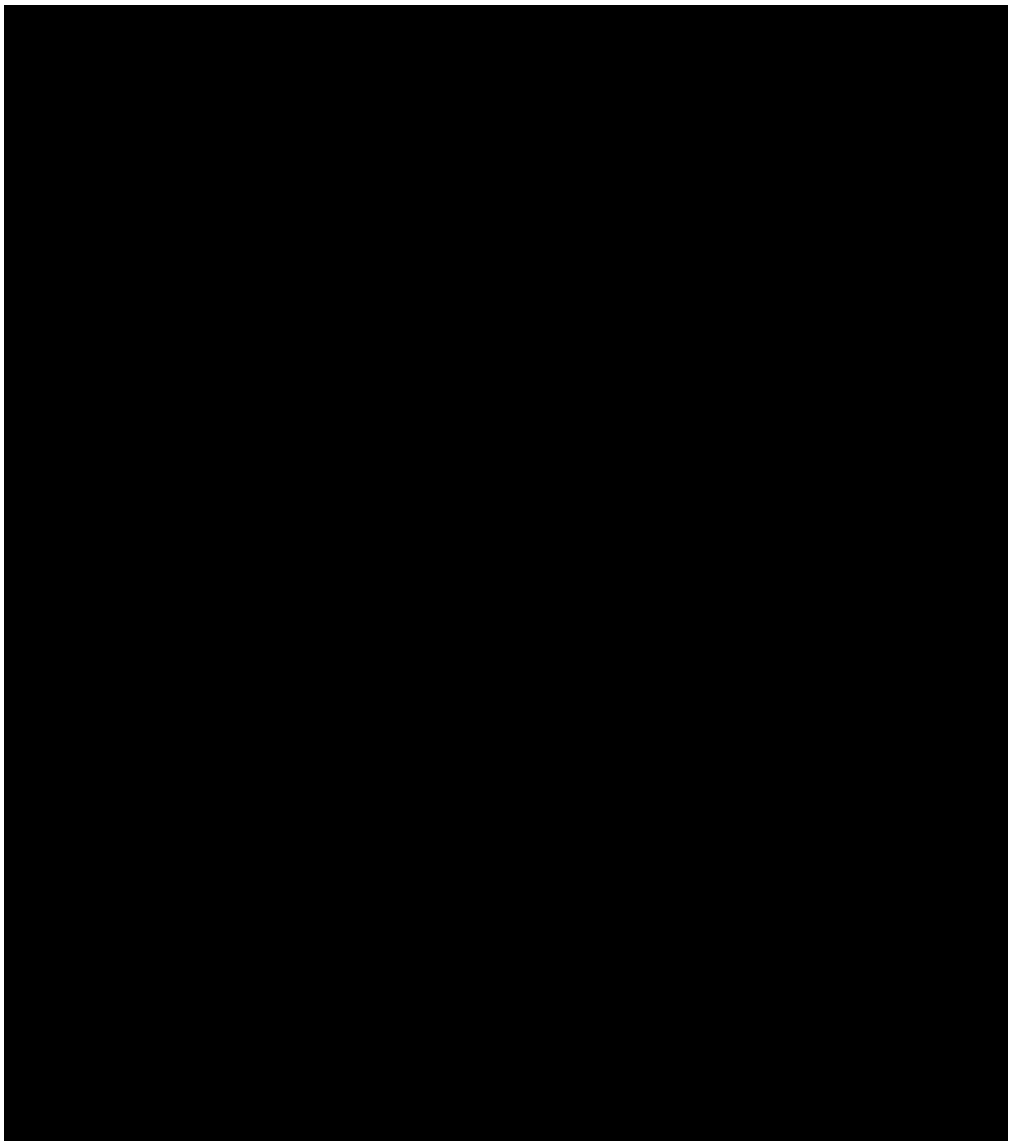
While completing the questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim.* If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what *they* think the questions mean.

General information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential and will be treated

as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

The investigator must complete the patient/visit information on the PRO and ensure that the center number, patient's number and initials are identical to the Case Record Form. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.



16.9 Appendix 10: Environmental factors related to ASAS Health Index

Environmental factors related to ASAS Health Index

Date: _____
Name: _____

Please answer all statements by placing one check mark per statement to indicate which response best applies to you **at this moment in time** taking into account your rheumatic disease (the term "rheumatic disease" contains all forms of spondyloarthritis including ankylosing spondylitis).

As a result of my rheumatic disease, my family / relatives take more responsibility for household tasks.

☐ I agree

☐ I do not agree

I don't like the way my friends act around me.

☐ I agree

☐ I do not agree

I cannot count on my relatives to help me with my problems.

☐ I agree

☐ I do not agree

I modify my home and work environments.

☐ I agree

☐ I do not agree

I have difficulties getting worsening of my disease acknowledged by a health care professional.

☐ I agree

☐ I do not agree

Treatment of my rheumatic disease is taking up time.

☐ I agree

☐ I do not agree

My friends expect too much of me.

☐ I agree

☐ I do not agree

No one pays much attention to me at home.

☐ I agree

☐ I do not agree

My friends understand me.

☐ I agree

☐ I do not agree

Thank you for answering this questionnaire.

Developed by Assessment of SpondyloArthritis International Society (ASAS)