NOVARTIS

Clinical Development - Medical Affairs Region Europe

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457H3301 / NCT03136861

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

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List of abbreviations

ACR	Albumin-Creatinine Ratio
AE	Adverse Event
ADR	Adverse Drug Reaction
ALP	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic Pyruvic Transaminase
ANOVA	Analysis of Variance
anti-TNFα	anti-Tumor Necrosis Factor alpha
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase
ATC	Anatomical Therapeutic Classification
axSpA	axial SpondyloArthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
CD	Cluster of Differentiation
CI	Confidence Interval
COX-1	CycloOXygenase-1
COX-2	CycloOXygenase-2
CPO	Country Pharma Organization
CRF	Case Report Form
CRO	Contract Research Organization
DS&E	Drug Safety and Epidemiology
DMARDs	Disease Modifying Antirheumatic Drugs
eCRF	electronic CRF
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
EU	European Union
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS-TP1	Full Analysis Set for Treatment Period 1
FAS-TP2	Full Analysis Set for Treatment Period 2
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γGT	Gamma Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA-B27	Human Leukocyte Antigen-B27
hsCRP	high sensitivity C-Reactive Protein
IB	Investigator's Brochure
IBP	Inflammatory Back Pain
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for

	Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions For Use
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio (for blood clotting times)
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	Intravenous
LFT	Liver Function Test (raised serum transaminase and/or bilirubin levels)
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
nr-axSpA	non-radiographic axial SpondyloArthritis
NSAID(s)	Nonsteroidal Anti-Inflammatory Drug(s)
NRS	Numerical Rating Scale
PASS	Patient Accepted Symptoms State
PCR	Protein-Creatinine Ratio
PFS(s)	PreFilled Syringe(s)
PRN	Pro re nata (as needed)
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
PT	Preferred Term
PT/INR	Prothrombin Time/ International Normalized Ratio
QoL	Quality of Life
SAE	Serious Adverse Event
SAF-TP1	Safety Set for Treatment Period 1
SAF-TP2	Safety Set for Treatment Period 2
s.c.	Subcutaneous
SIJ	Sacroiliac Joints
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SpA	SpondyloArthritis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBL	Total Bilirubin
TNF	Tumor Necrosis Factor
TNFα-IR	Tumor Necrosis Factor α Inadequate Responder
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the patient in a time unit
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Inadequate response to TNFα	Active disease despite stable treatment with anti-tumor necrosis factor alpha (TNFα) for at least 3 months at an approved dose or for at least one dose in the case of lack of tolerance
Medication number	A unique identifier on the label of each study treatment package in studies that dispense study treatment
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study
Period	A portion of the study that serves a specific purpose. Typical periods are: Screening, treatment, and follow-up
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
Study treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CAIN457H3301
Full Title	A 24-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in controlling spinal pain in patients with axial spondyloarthritis
Brief title	SKIPPAIN – **S**peed of onset of Secu**K**inumab-**I**nduced relief from **P**ain in **P**atients with **A**x**I**al Spo**N**dyloarthritis
Sponsor and clinical phase	Novartis, Phase IIIb
Investigation type	Drug; biological
Study type	Interventional
Purpose and rationale	The majority of patients with axial spondyloarthritis (axSpA) experience inflammatory back pain (IBP) as the first symptom of disease and the burden of pain is comparable for patients with non-radiographic axSpA (nr-axSpA) and ankylosing spondylitis (AS). Most patients with axSpA also experience severe fatigue, which has been shown to be deeply influenced by pain. It has been reported how pain, disease activity, fatigue and disease flares affect the quality of life (QoL) of patients with axSpA. According to treat-to-target recommendations for patients with spondyloarthritis (SpA), the primary goal of the treatment is to maximize long-term health-related QoL and social participation through control of signs and symptoms, including pain. In addition, improvement of disease activity and fatigue, as well as the achievement of a stable disease status with control of disease flares, are considered key targets of the treatment strategy. Therefore, the fast onset in pain relief is one of the most relevant outcomes for patients with axSpA determining individual QoL. In order to address these unmet patient needs, this double-blind, randomized, parallel-group, placebo-controlled study is primarily assessing the efficacy of secukinumab 150 mg compared to placebo in terms of significant relief from spinal pain, as measured by a numerical rating scale (NRS < 4), as early as Week 8. The cut-off value of NRS < 4 has been chosen in accordance with the cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. In addition, improvement in disease activity, fatigue and assessment of disease flares will be evaluated at Week 8 and/or Week 12 and at Week 24. At Week 8, patients randomized to either secukinumab or placebo treatment at Baseline will be re-randomized to active treatment with secukinumab 150 mg or 300 mg. Re-randomization will provide patients with the maximal opportunity to respond to secukinumab treatment. The potential benefit of dose escalation from secukinumab 150 mg to 300 mg will be explored during Treatment Period 2 (Week 8 to Week 24) in a proportion of patients assigned to secukinumab 150 at Baseline who did not achieve a response (i.e. spinal pain < 4) at Week 8. Similarly, a proportion of patients in the placebo group will be assigned secukinumab 300 mg during Treatment Period 2 so as to explore how those patients respond to a higher starting dose of secukinumab.

Primary objective	• To assess the superiority of secukinumab 150 mg compared to placebo in achieving a spinal pain score < 4 on a 0-10 NRS at Week 8.
Secondary objective	• To assess the superiority of secukinumab 150 mg compared to placebo in achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score < 4 at Week 8.
Exploratory objectives	• Proportion of patients achieving a spinal pain score < 4 on a 0-10 NRS at Week 1, 2, 3 and 4 with secukinumab 150 mg compared to placebo. • Proportion of patients in each treatment arm achieving a spinal pain score < 4 on a 0-10 NRS at Week 24. • Proportion of patients in each treatment arm achieving a BASDAI score < 4 at Week 24. • Proportion of patients in each treatment arm achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) score < 2.1 at Week 8 and Week 24. • Proportion of patients in each of treatment arm achieving ASDAS score < 1.3 at Week 8 and Week 24. • Mean change from Baseline in functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue©) score in patients on secukinumab 150 mg compared to placebo at Week 8. • Mean change from Baseline in FACIT-Fatigue© score in each treatment arm at Week 24. • Proportion of patients in Arm A1 who have pain flares defined as NRS score > 6 at Week 12 or Week 24. • Proportion of patients achieving a satisfactory Patient Acceptable Symptom State (PASS) at Week 1, 2, 3, 4 and 8 with secukinumab 150 mg compared to placebo. • Proportion of patients in each treatment arm achieving a satisfactory PASS at Week 12, Week 20 and Week 24. • Spinal pain NRS score according to previous exposure to tumor necrosis factor (TNF) blockers at Week 1, 2, 3, 4, 8, 12 and 24. • Proportion of patients achieving a spinal pain score < 4 on a 0-10 NRS for TNF-naïve patients compared to TNFα-inadequate responder (TNFα-IR) patients at Week 8 and Week 24. • Proportion of patients who responded to secukinumab 150 mg at Week 8 (i.e. spinal pain score < 4 on a 0-10 NRS) maintaining a response at Week 24. • Proportion of patients achieving an improvement in Assessment of SpondyloArthritis International Society (ASAS) health index with secukinumab 150 mg compared to placebo at Week 8. • Proportion of patients achieving an improvement in ASAS health index in each treatment arm at Week 24. • ASAS health index at Week 8 and Week 24. • Change from baseline in total NRS score at all time points. • Change from baseline in total BASDAI score at all time points. • ASDAS-CRP at Week 8 and Week 24. • [redacted] • Safety and tolerability of secukinumab 150 mg and 300 mg over

	the study period.
Study design	This is a 24-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in controlling spinal pain in patients with axSpA. The study will consist of 2 treatment periods; a double-blind, placebo-controlled period from Baseline to time of study drug administration at Week 8 during which patients will be randomized to secukinumab 150 mg or placebo; followed by a double-blind secukinumab treatment period from Week 8 to Week 24 during which patients will be re-randomized to 1 of 5 treatment arms to receive either secukinumab 150 mg or secukinumab 300 mg. Patients assigned to secukinumab 150 mg (Group A) at Baseline who are responders (i.e. spinal pain score < 4) at Week 8 will continue on the same dose until Week 24 under 1 treatment arm (Arm A1). Patients assigned to secukinumab 150 mg at Baseline who are non-responders at Week 8 will be re-randomized to 1 of 2 treatment arms: secukinumab 150 mg (Arm A2) or secukinumab 300 mg (Arm A3) from Week 8 to Week 24. Similarly, patients assigned to placebo (Group B) at Baseline will be re-randomized to 1 of 2 treatment arms: secukinumab 150 mg (Arm B1) or secukinumab 300 mg (Arm B2) from Week 8 until Week 24.
Population	Male and female patients ≥ 18 years of age (at the time of consent) with axSpA diagnosis (either AS or nr-axSpA) fulfilling the ASAS criteria. Patients must have clinical signs of spinal involvement defined by presence of IBP with active disease defined by BASDAI score ≥ 4, spinal pain NRS score > 4 and inadequate response (including intolerance) to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) over a 4-week period, unless contraindicated. Patients will be allowed to continue background medications (including NSAIDs, selected disease modifying anti-rheumatic drugs (DMARDs), i.e. methotrexate (MTX) and sulfasalazine, and corticosteroids) in this study in accordance with the protocol sections on concomitant and prohibited medications.
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-nursing female patients at least 18 years of age with 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** • Human Leukocyte Antigen-B27 (HLA-B27) positive with ≥ 2 SpA features. 3. Active axSpA as assessed by total BASDAI score ≥ 4 at Baseline. 4. Spinal pain NRS score > 4 at Baseline. 5. 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 contraindication. 6. 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 2 weeks before randomization. 7. Patients who have previously on a TNFα inhibitor will be allowed entry into study after an appropriate what-out period prior to randomization: • 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route) • 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion) • 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route) • 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days • 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days
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 magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months of Screening and evaluated by a qualified physician (otherwise chest X-ray or MRI is required to be performed at Screening). 2. Previous treatment with prohibited medication as outlined in Section 5.5.7 and Section 5.5.8 of the main protocol. Prohibited medication may be washed out before randomization in accordance with Section 5.5.7 and Section 5.5.8 of the main protocol. 3. Previous exposure to secukinumab or any other biologic drug directly targeting interleukin-17 (IL-17) or interleukin-23 (IL-23). 4. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer. 5. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes. 6. Patients previously treated with any biological immunomodulating agents, except those targeting TNFα. 7. Patients who have been exposed to more than one anti-tumor necrosis factor alpha (anti-TNFα) agent 8. Previous treatment with any cell-depleting therapies including but not limited to anti-cluster of differentiation (CD)20 or investigational agents (e.g. Campath®, anti-CD4, anti-CD5, anti-CD3, anti-CD19). 9. 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. 10. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire study or longer if required by locally approved prescribing information (e.g. 20 weeks since last dose of secukinumab in the European Union (EU)). 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) or tubal ligation at least 6 weeks before taking study treatment. 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) with spermicidal foam/gel/film/cream/vaginal suppository. • Use of oral, 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. • Placement of an intrauterine device or intrauterine system. In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal or not of childbearing 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) 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 childbearing potential. 11. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy (such as inflammatory bowel disease and uveitis). 12. Other ongoing mechanical diseases affecting the spine (such as severe osteoarthritis of spine and diffuse idiopathic skeletal hyperostosis and fibromyalgia) that may confound evaluation of the benefit of secukinumab therapy. 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), uncontrolled diabetes, or very poor functional status (unable to perform self-care). 15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase/ serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT),

	alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria: • Any single parameter may not exceed 2 × upper limit of normal (ULN). A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error. • If the total bilirubin concentration is increased above 2 × 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 1.5 mg/dL (132.6 µmol/L). 17. Screening total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL (85 g/L). 18. Active systemic infections during the last 2 weeks prior to randomization (exception: common cold). 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. 20. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or 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 keratosis 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. Any current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial. 23. 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. 24. History or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization. 25. Administration of live vaccines 6 weeks prior to randomization or plans for administration of live vaccines during the study period; live vaccines should not be given until 12 weeks after last study treatment administration.
Study treatment	Secukinumab 150 mg will be provided in 1 mL prefilled syringes (PFSs) for s.c. injection. Secukinumab 300 mg will be provided as 2 PFSs each containing 150 mg secukinumab. Secukinumab placebo will be provided as 1 mL PFS. **Treatment Period 1 (Baseline to Week 8)** At Baseline, all patients whose eligibility is confirmed will be randomized in a 3:1 ratio to secukinumab 150 mg or placebo as shown below. Patients

	will be stratified at randomization according to previous exposure to TNF blockers (i.e. according to whether they are naïve to TNFα inhibitors or are TNFα-IR patients. **Group A: secukinumab 150 mg** • Secukinumab 150 mg (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4 **Group B: placebo** • Placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4 **Treatment Period 2 (Week 8 to Week 24)** At Week 8, patients randomized to Group A (secukinumab 150 mg) at Baseline will be classified as responders (spinal pain NRS score < 4) or non-responders (spinal pain NRS score ≥ 4) based on their spinal pain scores and re-randomized to 1 of 3 treatment arms to receive either secukinumab 150 mg or 300 mg. Those patients randomized to Group B (placebo) at Baseline will be re-randomized to 1 of 2 treatment arms to receive either secukinumab 150 mg or 300 mg at Week 8. *Responders in Group A (spinal pain NRS score < 4):* • **Arm A1**: secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20 *Non-responders in Group A (spinal pain NRS score ≥ 4):* • **Arm A2:** secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20 • **Arm A3:** secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20 Patients randomized to placebo (Group B) at Baseline will be re-randomized to secukinumab 150 mg or 300 mg at Week 8: • **Arm B1:** secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20 • **Arm B2:** secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20 Patients will be allowed to continue background medications during the study in accordance with the protocol sections on concomitant and prohibited medications.
Efficacy assessments	• Spinal pain NRS assessment • BASDAI • ASDAS • FACIT-Fatigue© • PASS • ASAS Health Index
Safety assessments	• Evaluation of adverse events (AEs) and serious adverse events (SAEs) including injection site reactions • Physical examination • Vital signs • Laboratory evaluations (hematology, clinical chemistry and

	urinalysis)
Data analysis	The primary efficacy endpoint is the proportion of patients with a spinal pain NRS score < 4 at Week 8. The primary analysis will be performed comparing treatments with respect to the primary efficacy endpoint in a logistic regression model with the factors treatment, country and the stratification factor (naïve/ inadequate responders to TNFα inhibitors). The odds ratio and its 95% confidence interval (CI) and p-value will be given. For the primary endpoint, patients with missing assessments at Week 8 will be considered as non-responders. The raw spinal pain NRS scores will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will include the same factors as the logistic model above plus the baseline score as a covariate. The secondary efficacy endpoint, the proportion of patients with a BASDAI score < 4 at Week 8, will be analyzed similarly to the primary endpoint.
Key words	Axial spondyloarthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, inflammatory back pain, spinal pain, secukinumab, AIN457

1 Introduction

1.1 Background

Axial spondyloarthritis (axSpA) is a group of rheumatic disorders with spinal inflammation and inflammatory back pain (IBP) as typical hallmarks. The prevalence of axSpA is up to 1-2% in the Caucasian population (Braun et al 2011). Patients with chronic back pain (onset before 45 years of age) are classified according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA if they fulfill either the clinical arm or the imaging arm of the criteria (Rudwaleit et al 2009a).

Patients with axSpA are classified into ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA) based on the presence or absence of sacroiliitis on conventional X-ray radiographs according to the 1984 modified New York diagnostic criteria (van der Linden et al 1984). Patients with presence of sacroiliitis on X-ray are classified as having AS whereas patients with absence of sacroiliitis on X-ray but presence of inflammatory lesions in the sacroiliac joints (SIJ) on a magnetic resonance imaging (MRI) scan may be classified as having nr-axSpA.

Studies and registry data have shown that patients with nr-axSpA have a similar burden of disease to patients with AS in terms of pain, fatigue and impairment of health-related quality of life (QoL) (Wallis et al 2013). Disease parameters and response rates to treatment with tumor necrosis factor (TNF) antagonists are similar in patients with AS and nr-axSpA, supporting the concept that axSpA may represent a disease with distinct stages (Song et al 2013).

The majority of patients with axSpA experience IBP as the first symptom of the disease. According to ASAS criteria, IBP is defined as chronic back pain (lasting longer than 3 months) where 4 out of the following 5 parameters are present: 1) age at onset is below 40 years, 2) insidious onset, 3) causes pain at night with improvement upon getting up, 4) improves with exercise but 5) does not improve at rest. As reported in one study (Rudwaleit et al 2006), IBP usually improves with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Recent studies also demonstrated how spinal pain strongly correlates with QoL measured by the ASQoL questionnaire. Spinal pain also strongly correlates with disease duration and Short Form-36 questionnaire sub-scales (Bodur et al 2011).

Fatigue is another major clinical feature of rheumatic diseases and is defined as a state of reduced muscle capacity and decreased work ability accompanied by feelings of tiredness, weariness, and lack of energy (Missaoui and Revel 2006). A recent study by Bedaiwi et al (2015) demonstrated that 67.3% of patients with axSpA had severe fatigue, and that patients with AS and nr-axSpA were equally affected. Brophy et al 2013 demonstrated how fatigue is deeply influenced by pain. In fact, according to the findings of this study, the measures to address fatigue in AS need to focus primarily on the pain rather than anxiety, physical activity, motivation, or sleep. Pain is the single factor examined that contributes to explaining the variation in fatigue. Treatment with anti-tumor necrosis factor therapy may improve levels of pain and fatigue; however, the majority of patients with axSpA may still

experience significant residual pain (mean 54.4 on a scale of 0-100) and fatigue (mean 51.8 on a scale of 0-100) while on treatment.

Secukinumab (AIN457) is a recombinant high-affinity fully human monoclonal anti-human Interleukin-17A (IL-17A) antibody of the IgG1-κ class. IL-17A is mainly produced by memory cluster of differentiation (CD)4+ and CD8+ T lymphocytes and is one of the principal pro-inflammatory cytokines in AS as well as other immune mediated inflammatory diseases such as psoriasis, and psoriatic arthritis (PsA). Secukinumab is selective for human IL-17A and potently neutralizes the bioactivity of this cytokine. Secukinumab is marketed as Cosentyx® in more than 60 countries worldwide (including Europe and the US) and is available as solution in different doses for subcutaneous (s.c.) injection. The product is indicated for the treatment of AS (the recommended dose is 150 mg), PsA (the recommended dose is 150 mg; however, for patients who are TNFα inadequate responders (TNFα-IR) or have concomitant moderate to severe psoriasis, the recommended dose is 300 mg) and moderate to severe plaque psoriasis (the recommended dose is 300 mg).

Secukinumab has demonstrated improvements in total spinal pain compared to placebo in Phase III studies in patients with AS at all time points from Baseline to Week 16, and improvements observed at Week 16 were sustained up to Week 52. Secukinumab also led to greater reductions than placebo with regard to the change from Baseline in functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue©) scale total score at all time points assessed from Week 4 to Week 16. However, besides the insights for secukinumab efficacy generated so far, data derived from a controlled and blinded study with a dedicated primary objective assessing pain levels as a potential decision-maker for further treatment options after a relatively short exposure to secukinumab are currently not available.

1.2 Purpose

The purpose of the study is to evaluate the efficacy and safety of secukinumab 150 mg compared to placebo in the early management (Baseline to Week 8) of spinal pain, disease activity, fatigue and predictability of disease flares in patients with axSpA who have an inadequate response to prior NSAIDs. This study will also assess the efficacy and safety of secukinumab 300 mg compared to secukinumab 150 mg from Week 8 to Week 24 in order to assess the potential additional benefits of dose escalation in patients with axSpA.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Objectives and related endpoints for the study are described in Table 2-1. Note: the treatment arms referred to in Table 2-1 are defined in Section 5.2.

Table 2-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Primary endpoint**
• To assess the superiority of secukinumab 150 mg compared to placebo in achieving a spinal pain score < 4 on a 0-10 numerical rating scale (NRS) at Week 8.	• Proportion of patients with a spinal pain NRS score < 4 at Week 8 in Group A compared to Group B.
Secondary objective	**Secondary endpoints**
• To assess the superiority of secukinumab 150 mg compared to placebo in achieving a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score < 4 at Week 8.	• Proportion of patients with a BASDAI score < 4 at Week 8 in Group A compared to Group B.
Exploratory objectives	**Exploratory endpoints**
• Proportion of patients achieving a spinal pain score < 4 on a 0-10 NRS at Week 1, 2, 3 and 4 with secukinumab 150 mg compared to placebo.	• Proportion of patients with a spinal pain NRS score < 4 in Group A compared to Group B at Week 1, 2, 3 and 4.
• Proportion of patients in each treatment arm achieving a spinal pain score < 4 on a 0-10 NRS at Week 24.	• Proportion of patients with a spinal pain NRS score < 4 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
• Proportion of patients in each treatment arm achieving BASDAI score < 4 at Week 24.	• Proportion of patients achieving a BASDAI score < 4 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
• Proportion of patients in each of the treatment arms achieving Ankylosing Spondylitis Disease Activity Score (ASDAS) score < 2.1 at Week 8 and Week 24.	• Proportion of patients with a ASDAS score < 2.1 in Group A compared to group B at Week 8 and in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 8 and Week 24.
• Proportion of patients in each treatment arm achieving ASDAS score < 1.3 at Week 8 and Week 24.	• Proportion of patients with a ASDAS score < 1.3 in Group A compared to Group B at Week 8 and in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 8 and Week 24.
• Mean change from Baseline in functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue©) score in patients on secukinumab 150 mg compared to placebo at Week 8.	• FACIT-Fatigue© score in Group A compared to Group B at Week 8.

Objectives	Endpoints
• Mean change from Baseline in FACIT-Fatigue© score in each of treatment arm at Week 24.	• FACIT-Fatigue© score in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2 at Week 24.
• Proportion of patients in Arm A1 who have pain flares defined as NRS score > 6 at Week 12 or Week 24.	• Proportion of patients who have pain flares, defined as NRS score > 6, in Arm A1 at Week 12 or Week 24.
• Proportion of patients achieving a satisfactory Patient Acceptable Symptom State (PASS) at Week 1, 2, 3, 4 and 8 with secukinumab 150 mg compared to placebo.	• Proportion of patients achieving a satisfactory PASS at Week 1, 2, 3, 4 and 8 in Group A compared to Group B.
• Proportion of patients in each of treatment arm achieving a satisfactory PASS at Week 12, Week 20 and Week 24.	• Proportion of patients achieving a satisfactory PASS at Week 12, Week 20 and Week 24 in Arm A1, Arm A2 vs Arm A3, and Arm B1 vs Arm B2.
• Spinal pain NRS score according to previous exposure to tumor necrosis factor (TNF) blockers at Week 1, 2, 3, 4, 8, 12 and 24.	• Proportion of patients achieving a spinal pain score < 4 in TNF-naïve and TNF-exposed subgroups at Week 1, 2, 3, 4, 8, 12 and 24.
• Proportion of patients achieving a spinal pain score < 4 on a 0-10 NRS for TNF-naïve patients compared to TNFα-IR patients at Week 8 and Week 24.	• Proportion of patients achieving a spinal pain score < 4 for TNF-naïve patients compared to TNFα-IR patients at Week 8 and Week 24
• Proportion of patients who responded to secukinumab 150 mg at Week 8 (i.e. spinal pain score < 4 on a 0-10 NRS) maintaining a response at Week 24.	• Proportion of patients with spinal pain score < 4 on a 0-10 NRS at Week 8 maintaining a spinal pain score < 4 at Week 24.
• Proportion of patients achieving an improvement in ASAS health index with secukinumab 150 mg compared to placebo at Week 8.	• Proportion of patients achieving an improvement in ASAS health index with secukinumab 150 mg compared to placebo at Week 8.
• Proportion of patients achieving an improvement in ASAS health index in each treatment arm at Week 24.	• Proportion of patients achieving an improvement in ASAS health index in each treatment arm at Week 24.
• ASAS health index at Week 8 and Week 24.	• Mean ASAS health index score in each treatment arm at Week 8 and Week 24
• Change from baseline in total spinal pain NRS score at all time points.	• Total spinal pain NRS score in each treatment arm at all time points.
• Change from baseline in total BASDAI score at all time points.	• Total BASDAI score in each treatment arm at all time points.
• ASDAS-CRP at Week 8 and Week 24.	• Mean ASDAS-CRP in each treatment arm at Week 8 and Week 24.
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• Safety and tolerability of secukinumab 150 mg and 300 mg over the study period.	• Adverse Events (AEs) and adverse drug reactions (ADRs) over the study period.

3 Investigational plan

3.1 Study design

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

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

At Baseline, all patients whose eligibility is confirmed will be randomized in a 3:1 ratio to secukinumab 150 mg or placebo as described below. Patients will be stratified at randomization according to previous exposure to TNF blockers (i.e. according to whether they are naïve to TNFα inhibitors or are TNFα-IR patients) to ensure a comparable number of patients for each subgroup. It is assumed that approximately one third of the randomized patients will be TNFα-IR.

The primary endpoint of this study is spinal pain at Week 8. At Week 8, patients randomized to Group A (secukinumab 150 mg) at Baseline will be assessed as responders (spinal pain NRS score < 4) or non-responders (spinal pain NRS score ≥ 4) based on their spinal pain scores. Responders will be re-assigned to 1 treatment arm to continue secukinumab 150 mg (Arm A1) from Week 8 until Week 24. Non-responders will be separately re-randomized to 1 of 2 treatment arms to receive either secukinumab 150 mg (Arm A2) or secukinumab 300 mg (Arm A3) from Week 8 until Week 24. At Week 8, patients randomized to Group B (placebo) at Baseline will be separately re-randomized to 1 of 2 treatment arms to receive either secukinumab 150 mg (Arm B1) or secukinumab 300 mg (Arm B2) from Week 8 until Week 24. A schematic of the study design is presented in Figure 3-1.

3.1.1 Treatment Period 1

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

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

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

3.1.2 Treatment Period 2

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

- Patients on secukinumab 150 mg who achieve spinal pain NRS score < 4 at Week 8 will be re-assigned to continue secukinumab 150 mg every 4 weeks (Arm A1)
  - **Arm A1**: secukinumab 150 mg (1 x 1.0 mL) plus placebo (1 x 1.0 mL) administered at Week 8, 12, 16 and 20
- Patients on secukinumab 150 mg who do not achieve spinal pain NRS score < 4 at Week 8 will be re-randomized to continue secukinumab 150 mg every 4 weeks (Arm A2) or to escalate to secukinumab 300 mg every 4 weeks (Arm A3):
  - **Arm A2**: secukinumab 150 mg (1 x 1.0 mL) plus placebo (1 x 1.0 mL) administered at Week 8, 12, 16 and 20
  - **Arm A3**: secukinumab 300 mg (2 x 1.0 mL) administered at Week 8, 12, 16, and 20

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

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

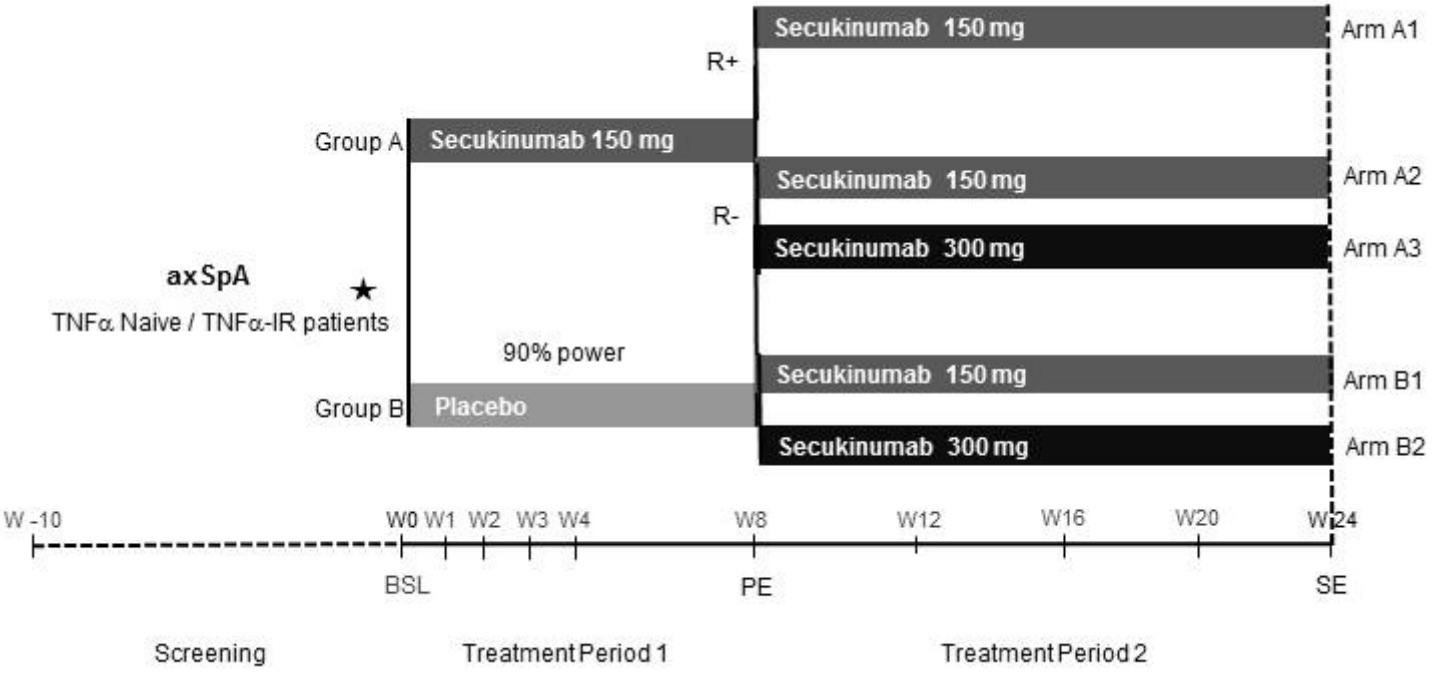
During the study, patients will be required to self-administer secukinumab or placebo at all study visits and at home at Week 16 (see Table 6-1 and Table 6-2 for the timing of study treatment administration).

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

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

Patients will be allowed to continue background medications in accordance with Section 5.5.7 (concomitant medications) and Section 5.5.8 (prohibited medications). For patients taking NSAIDs, intake will be recorded according to ASAS recommendations for collecting, analyzing and reporting NSAID intake (Appendix 10).

Figure 3-1 Study design



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

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

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

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

[redacted]

3.2 Rationale for study design

The majority of patients with axSpA experience IBP as the first symptom of the disease and the burden of pain is comparable for patients with nr-axSpA and AS. Most patients with axSpA also experience severe fatigue, which has been shown to be deeply influenced by pain. It has been reported how pain, disease activity, fatigue, and disease flares affect the QoL of patients with axSpA. According to treat-to-target recommendations for patients with spondyloarthritis (SpA), the primary goal of the treatment is to maximize long-term health-related QoL and social participation through control of signs and symptoms, including pain (Smolen et al 2014). In addition, improvement of disease activity and fatigue, as well as the achievement of a stable disease status with control of disease flares are considered key targets of the treatment strategy (Wendling 2015).

However, besides the insights for secukinumab efficacy generated so far, data derived from a controlled and blinded study with a dedicated primary objective assessing pain levels as a potential decision-maker for further treatment options after a relatively short exposure to secukinumab are currently not available.

In order to address these unmet medical needs, this double-blind, randomized, parallel-group, placebo-controlled study will primarily assess the efficacy of secukinumab 150 mg compared to placebo in providing a significant relief from spinal pain, as measured by spinal pain NRS score < 4, as early as Week 8. The cut-off value of spinal pain NRS < 4 has been chosen in accordance with the accepted cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain (Boonstra et al 2014). In addition, improvement in disease activity, fatigue and assessment of disease flares will be evaluated at Week 8 and/or Week 12 and at Week 24 to monitor pain levels after the early drug response to secukinumab for all patients.

The treatment duration of the placebo group has been considered to have the appropriate length to ensure the reliable evaluation of the primary endpoint. At Week 8, patients randomized to either secukinumab or placebo treatment at Baseline will be re-randomized to active treatment with secukinumab 150 mg or 300 mg. Re-randomization will be performed to provide all patients with the maximal opportunity to respond to secukinumab treatment (Section 3.5).

In order to accomplish treat-to-target recommendations for the management of SpA (Smolen et al 2014), a proportion of non-responder patients (i.e. patients not responding to 8 weeks of treatment with secukinumab 150 mg) will be assigned to an escalated dose of secukinumab (i.e. 300 mg) for 16 weeks (i.e. from Week 8 to Week 24) with the aim of exploring potential additional benefits in treatment adjustment and optimization. In addition, a proportion of patients from the placebo group will be assigned secukinumab 300 mg from Week 8 to Week 24 so as to explore the potential benefits of a higher dose of secukinumab (Section 3.3).

The regular assessments of disease activity ensure that safety will be monitored closely and both the patient and the investigator will have the opportunity to assess if the patient's continued participation in the study is to his/her benefit. If the patient's participation is

deemed not to be of benefit to him/her, the patient can exit the study at any time (see Section 5.6.2).

This study has been discussed by a Patient Associations' Steering Committee to guarantee that the study endpoints and the study conduct are fully aligned with patients' expectations and unmet clinical needs from a patient's perspective. The stratification criterion was chosen because previous TNFα exposure can have an influence on secukinumab response (Baeten et al 2015), and therefore allows for a balanced distribution between the verum and the placebo group.

3.3 Rationale for dosing regimen, route of administration and duration of treatment

Although nr-axSpA is often regarded as a milder disease compared to AS, it has been demonstrated that the burden of the 2 diseases is similar in terms of pain and activity (Sieper et al 2013). As a consequence, the dose, dose regimen, formulation and route of administration of secukinumab are the same in these 2 populations.

The dose (150 mg and 300 mg), dose regimen (weekly from Baseline to Week 4, monthly from Week 8 to Week 20), formulation (liquid in PFSs) and route of administration (s.c.) for secukinumab used in this study are supported by the comprehensive AS clinical trial program (including the pivotal Phase 3 studies CAIN457F2305 and CAIN457F2310 (Baeten et al 2015) and the CAIN457F2320 study) that demonstrated the efficacy, tolerability and safety of secukinumab.

The potential additional benefit of dose escalation from secukinumab 150 mg to 300 mg will be explored during Treatment Period 2 (Week 8 to Week 24) in a proportion of patients assigned to secukinumab 150 at Baseline who did not achieve a response at Week 8. Similarly, a proportion of patients in the placebo group will be assigned secukinumab 300 mg during Treatment Period 2 so as to explore how those patients respond to a higher starting dose of secukinumab.

3.4 Rationale for choice of comparator

A placebo arm up to Week 8 is included in this study. Due to the nature of the disease and the outcome measures used (e.g. spinal pain NRS score as primary endpoint, and BASDAI score as secondary endpoint), a placebo arm is necessary to obtain reliable efficacy measurements for comparison between the active treatment group and placebo in a controlled fashion up to 8 weeks. The continuation of the placebo group up to Week 8 can be supported from an ethical standpoint, as patients continue their treatment with NSAIDs and other concomitant treatments including methotrexate (MTX) and sulfasalazine. In addition, regular and controlled assessment of pain and disease activity ensures that patients experiencing worsening of the disease in any treatment group can exit the study. Moreover, the inclusion of a placebo group is considered relevant for trials in nr-axSpA, in accordance with previously implemented methodology and in compliance with the European Medicines Agency (EMA/EMEA) guidelines for AS (CPMP/EWP/4891/03), and as recommended by the Food and Drug Administration (FDA).

3.5 Rationale for re-randomization of patients

Re-randomization will be performed to provide all patients with the maximal opportunity to respond to secukinumab treatment. Patients assigned to secukinumab 150 mg at Baseline who are responders (i.e. spinal pain score < 4) at Week 8 will be re-assigned to receive the same dose until Week 24 thereby providing the opportunity to confirm that patients sustain their treatment response until the end of the study. Patients assigned to secukinumab 150 mg at Baseline who are non-responders at Week 8, and all patients assigned to placebo at Baseline, will be re-randomized to secukinumab 150 mg or 300 mg from Week 8 until Week 24. Besides supporting the blinding strategy of the study, this provides patients who did not respond to active treatment during the first 8 weeks a further chance to respond to secukinumab over an additional 16 weeks and potential differences between the 2 treatment regimens can be explored. Patients on placebo until Week 8, whose bone structure may be impacted by the underlying chronic disease, will have the opportunity to have their chronic disease treated by active treatment with secukinumab for up to 16 weeks. The descriptive analysis of these data can help to understand the different combinations of response to explore further insights for the 2 treatment regimens.

3.6 Purpose and timing of interim analyses/design adaptations

Not applicable. No interim analysis or design adaptations are planned for this study.

3.7 Risks and benefits

As of June 2016, approximately 16,400 patients and healthy subjects have been enrolled in both completed and ongoing studies with secukinumab, with over 14000 having 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 across various indications including AS, psoriasis, rheumatoid arthritis, PsA, multiple sclerosis, uveitis, dry eye, Crohn's disease, asthma and polymyalgia rheumatica.

The risk profile of secukinumab in axSpA is informed by the safety data from the pivotal clinical trials in moderate to severe plaque psoriasis and the spondyloarthritides (e.g. PsA and AS). For these indications, secukinumab has shown a higher rate of total adverse events (AEs), mainly infections, when compared to placebo (placebo-controlled periods of 12 to 16 weeks depending on the protocol). The majority of infections were non-serious upper respiratory tract infections. However, no clinically meaningful difference was observed in infectious serious adverse events (SAEs). In addition, no dose dependency with secukinumab (300 mg and 150 mg) was observed in the overall rate of infections or upper respiratory tract infections.

Adverse drug reactions (ADRs) classified as very common (≥ 1/10 patients) or common (≥ 1/100 but < 1/10 patients) included upper respiratory tract infections (nasopharyngitis, upper respiratory tract infection, rhinitis and pharyngitis), oral herpes, rhinorrhea, diarrhea and urticaria. Uncommon (≥ 1/1000 but < 1/100 patients) ADRs included sinusitis, tonsillitis, oral candidiasis, tinea pedis, neutropenia and conjunctivitis.

Infections, neutropenia and hypersensitivity are important identified risks, while malignancies, major adverse cardiovascular events, immunogenicity, Crohn's disease, and hepatitis B

reactivation (Europe only) are important potential risks. Interaction with live vaccines is an important potential risk.

Immunogenicity was low with secukinumab and did not correlate with loss of efficacy in all indications studied to date.

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

The risk to patients in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance for the investigators provided in the Investigator's Brochure (IB). Additional safety information can also be found in the IB.

4 Population

The study population will consist of male and female patients (≥ 18 years old at the time of consent) with axSpA diagnosis, either AS or nr-axSpA fulfilling the ASAS criteria (Rudwaleit et al 2009a). Patients must report clinical signs of spinal involvement defined by presence of IBP with active disease defined by BASDAI score ≥ 4, spinal pain NRS score > 4 and an inadequate response to at least 2 NSAIDs (including intolerance) over at least a 4-week period, unless contraindicated.

The study aims to screen approximately 423 patients in order to randomize approximately 352 patients across the participating countries.

4.1 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-nursing female patients at least 18 years of age with diagnosis of axSpA (either AS or nr-axSpA) according to ASAS axSpA classification criteria (Appendix 4) to be applied in patients with back pain for at least 3 months and age of onset < 45 years:
    - Sacroiliitis on imaging (see Appendix 6) with ≥ 1 SpA feature (see Appendix 4) **or**
    - Human Leukocyte Antigen-B27 (HLA-B27) positive with ≥ 2 SpA features (see Appendix 4).
3. Active axSpA as assessed by total BASDAI score ≥ 4 at Baseline.
4. Spinal pain NRS score > 4 at Baseline.
5. 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 contraindication.

6. Patients who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their axSpA therapy are required to be on a stable dose for at least 2 weeks before randomization.
7. Patients who have previously been on a TNFα inhibitor will be allowed entry into study after an appropriate wash-out period prior to randomization:
   - 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
   - 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
   - 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
   - 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
   - 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days

4.2 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 MRI with evidence of ongoing infectious or malignant process obtained within 3 months of Screening and evaluated by a qualified physician (otherwise chest X-ray or MRI is required to be performed at Screening).
2. Previous treatment with prohibited medication as outlined in Section 5.5.7 and Section 5.5.8. Prohibited medication may be washed out before randomization in accordance with Section 5.5.7 and Section 5.5.8.
3. Previous exposure to secukinumab or any other biologic drug directly targeting interleukin-17 (IL-17) or interleukin-23 (IL-23).
4. Use of any investigational drug and/or devices within 4 weeks of randomization, or a period of 5 half-lives of the investigational drug, whichever is longer.
5. History of hypersensitivity to the study drug or its excipients or to drugs of similar chemical classes.
6. Patients previously treated with any biological immunomodulating agents, except those targeting TNFα.
7. Patients who have been exposed to more than one anti-tumor necrosis factor alpha (anti-TNFα) agent.
8. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. Campath®, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
9. 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.
10. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during entire

study or longer if required by locally approved prescribing information (e.g. 20 weeks since last dose of secukinumab in the European Union (EU)). 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) or tubal ligation at least 6 weeks before taking study treatment. 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) with spermicidal foam/gel/film/cream/vaginal suppository.
- Use of oral, 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.
- Placement of an intrauterine device or intrauterine system.

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

Women are considered post-menopausal or not of childbearing 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) 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 childbearing potential.

11. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefit of secukinumab therapy (such as inflammatory bowel disease and uveitis).
12. Other ongoing mechanical diseases affecting the spine (such as severe osteoarthritis of spine and diffuse idiopathic skeletal hyperostosis and fibromyalgia) that may confound evaluation of the benefit of secukinumab therapy.
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), uncontrolled diabetes, or very poor functional status (unable to perform self-care).

15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 × upper limit of normal (ULN). A single parameter elevated up to and including 2 × ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out laboratory error.
    - If the total bilirubin concentration is increased above 2 × 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 1.5 mg/dL (132.6 µmol/L).
17. Screening total white blood cell (WBC) count < 3000/µL, or platelets < 100 000/µL or neutrophils < 1,500/µL or hemoglobin < 8.5 g/dL (85 g/L).
18. Active systemic infections during the last 2 weeks prior to randomization (exception: common cold).
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.
20. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or 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 keratosis 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. Any current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial.
23. 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.
24. History or evidence of ongoing alcohol or drug abuse within the last 6 months before randomization.
25. Administration of live vaccines 6 weeks prior to randomization or plans for administration of live vaccines during the study period; live vaccines should not be given until 12 weeks after last study treatment administration.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis or a designated Contract Research Organization (CRO) will supply the following:

- Investigational treatment
  - AIN457 (secukinumab) 150 mg provided in a 1.0 mL PFS
- Matching placebo
  - AIN457 (secukinumab) placebo provided in a 1.0 mL PFS

The PFSs are packed in a double-blinded fashion. The study treatments will be labeled as follows:

- AIN457 150mg/1.0 mL/Placebo.

5.1.2 Additional treatment

During this study, NSAIDs, selected analgesics, selected disease-modifying anti-rheumatic drugs (DMARDs), i.e. MTX and sulfasalazine, and systemic corticosteroids are permitted as part of patients' routine medical care and will not be provided by Novartis.

Concomitant medications are described in Section 5.5.7 and prohibited medications are described in Section 5.5.8.

5.2 Treatment arms

At Baseline, all patients whose eligibility is confirmed will be randomized in a 3:1 ratio to secukinumab 150 mg or placebo as shown below. Patients will be stratified at randomization according to whether they are naïve to TNFα inhibitors or are TNFα-IR patients. The primary endpoint of this study is reduction of spinal pain at Week 8. At Week 8, patients randomized to Group A (secukinumab 150 mg) at Baseline will be assessed as responders (spinal pain NRS score < 4) or non-responders (spinal pain NRS score ≥ 4) based on their spinal pain scores. Responders will be re-assigned to secukinumab 150 mg (Arm A1) from Week 8 until Week 24. Non-responders will be separately re-randomized to 1 of 2 treatment arms to receive either secukinumab 150 mg (Arm A2) or secukinumab 300 mg (Arm A3) from Week 8 to Week 24. At Week 8, patients randomized to Group B (placebo) at Baseline will be separately re-randomized to 1 of 2 treatment arms to receive either secukinumab 150 mg (Arm B1) or secukinumab 300 mg (Arm B2) from Week 8 to Week 24.

Group A: secukinumab 150 mg

Treatment Period 1

- Secukinumab 150 mg (1 × 1.0 mL prefilled syringe (PFS)) at Baseline, Week 1, 2, 3 and 4

Treatment Period 2

- Responders (spinal NRS score < 4):

  - **Arm A1:** secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20
- Non-responders (spinal pain NRS score ≥ 4):
  - **Arm A2:** secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20
  - **Arm A3:** secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20

Group B: placebo

Treatment Period 1

- Placebo (1 × 1.0 mL PFS) at Baseline, Week 1, 2, 3 and 4

Treatment Period 2

Patients randomized to placebo at Baseline will be re-randomized to secukinumab 150 mg or 300 mg at Week 8:

- **Arm B1:** secukinumab 150 mg (1 × 1.0 mL PFS) + placebo (1 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20
- **Arm B2:** secukinumab 300 mg (2 × 1.0 mL PFS) administered every 4 weeks from Week 8 to Week 20

Patients will be allowed to continue background medications in accordance with concomitant medication and prohibited medication (Section 5.5.7 and Section 5.5.8).

5.3 Treatment assignment and randomization

At Baseline, all eligible patients will be randomized to one of the treatment groups (Group A and Group B) via an Interactive Response Technology (IRT) system or similar system. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment group and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

Randomization at Baseline will be stratified based on prior TNFα inhibitor exposure (i.e. according to whether patients are TNFα inhibitor naïve or TNFα-IR). It is assumed that approximately one third of the randomized patients will be TNFα-IR.

At Week 8, patients randomized to Group A (secukinumab 150 mg) at Baseline will be assessed for the achievement of spinal pain NRS score and will be classified as responders (spinal pain NRS score < 4) or non-responders (spinal pain NRS score ≥ 4) and re-randomized or re-assigned via IRT to one of the treatment arms (Arm A1, Arm A2, Arm A3) as outlined in Section 5.2. At Week 8, patients randomized to Group B (placebo) at Baseline will be re-randomized via IRT to one of the 2 treatment arms (Arm B1 or Arm B2) as outlined in Section 5.2.

The IRT will be used to link the patient to a treatment group/arm and will specify unique medication numbers for the study drug to be dispensed to the patient. The randomization

numbers will not be communicated to the caller and will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be generated in collaboration with the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment groups/arms, which are in turn linked to medication numbers. A separate medication list will be produced in collaboration with Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drugs.

The randomization scheme for patients will be reviewed and endorsed by a statistical expert.

5.4 Treatment blinding

Patients, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Patient Number which is composed of the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Patient Number will not be re-used.

Upon signing the informed consent form (ICF), the patient will be assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the case report form (CRF) book with a matching Patient Number from the electronic data capture (EDC) system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening Period Study Disposition electronic CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label, which corresponds to placebo or active treatment. Investigator staff will identify the study drug packages to dispense to the patient by contacting the IRT and obtaining the medication numbers. Immediately before dispensing the packages to the patient, investigator staff will detach the outer parts of the labels from the packages and affix them to the source document (Drug Label Form) for that patient's unique Patient Number.

At Week 12, the investigator will dispense to the patient, supported by IRT, 2 study drug packages for home administrations at Week 16 (see Table 6-1). The investigator will detach the outer parts of the labels and affix them to the source documentation (Drug Label Page). Detailed instructions on the self-administration of the study treatment will be described in the Instructions for Use (IFU) provided to each patient and made available to the site staff and investigator. These instructions should be reviewed in detail by the patient and the site personnel.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

The study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator should educate the patient on how to properly store the study treatment when the patient is self-administering at home. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance or trial assigned Quality Assurance function.

The PFSs, which are sealed in their outer box, must be stored in a locked refrigerator between 2°C and 8°C (36°F and 46°F) and must be carefully controlled in accordance with regulations governing investigational medicinal products, local regulations and in accordance with instructions from the Novartis Drug Supply Management or Novartis Drug Supply Chain or corresponding service providers. The study drug should be protected from light and must not be frozen.

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 except for the medication number.

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.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Patients will self-administer the study treatment (secukinumab 150 mg, secukinumab 300 mg and placebo) by s.c. injection using 1 mL PFSs throughout the study. The dosing frequency will be either weekly or every 4 weeks in accordance with the administration schedule (Table 6-1 and Table 6-2).

Patients will receive instructions and training from study center staff on how to self-administer the study drug. Detailed instructions on the self-administration of the study treatment will be described in the IFU for secukinumab and provided to each patient. Patients will be asked to raise any questions and then to proceed with self-injection.

The injections scheduled to occur at the study center (i.e. Baseline, Week 1, Week 2, Week 3 and Week 4 during Treatment Period 1, and Week 8, Week 12 and Week 20 during Treatment Period 2) will be done by the patient (or caregiver) at the study center, under the supervision of the investigator or study staff.

The injection not scheduled to occur during a study center visit (i.e. Week 16 injection) will be done by eligible patients (or caregiver) at their home.

All doses prescribed and dispensed to the patient during the study must be recorded in the electronic CRF (eCRF).

Patients will be asked to document all doses and dates of self-administration at home in a self-administration log and are required to return this log to the study center at the visit following home administration (i.e. Visit 9/Week 20).

The investigator should promote compliance by instructing the patient to attend the study visits as scheduled and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

At the beginning of the study, the investigator/qualified study center staff will determine if self-administration is appropriate for the patient, e.g. manual dexterity, ability to follow the secukinumab PFS-IFU. If a patient requires a caregiver to administer study drug, the caregiver should be trained by the investigator/qualified study center staff. If a caregiver is not available at a particular visit or the patient is having problems with self-administration, the investigator/qualified study center staff may administer the study drug to the patient. However, all patients should be trained sufficiently and be comfortable with the study drug self-administration before the first home administration visit. Patients will be instructed to contact the investigator site staff in case of any issue during home administration of the study treatment.

Records of study drug kits assigned to the patient during the study must be documented.

At each visit, all study assessments, including the completion of PROs, should be completed prior to self-injection of the study drug.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Study treatment interruption is also not permitted with the following exceptions:

Study treatment interruption is permitted if, in the opinion of the investigator, a patient is deemed to be at a significant safety risk unless dosing 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 re-started after resolution of the safety risk. For additional points, please refer to Section 5.5.6.

Any study treatment interruption must be recorded on the corresponding eCRF page.

5.5.6 Allowed treatment modifications and escape treatment

Treatment modifications as well as new therapeutic interventions or a significant change to ongoing therapy must not be made before completion of Week 8 assessments.

Although no patient will be restricted from receiving necessary medications for lack of benefit or worsening of disease, if treatment with prohibited biologics (as described in Section 5.5.8) occurs, patients may remain in the trial but must discontinue study treatment. Efficacy will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based on safety and efficacy assessments or for any reason of their own accord will be free to discontinue participation in the study at any time (see Section 5.6.2).

As per Section 5.5.7, changes in non-biologic DMARDs and corticosteroids are permitted as per the investigator's clinical judgment after all Week 8 assessments are completed. However, it is recommended that these medications are continued at a stable dose from Week 8 through to Week 24. NSAIDs are to be administered in accordance with the posology and method of administration as described in the local Summary of Product Characteristics (SmPC).

Any treatment modifications or new therapeutic interventions must be recorded in the Concomitant medications eCRF page.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was 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 in the concomitant medications / significant non-drug therapies eCRF.

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.

5.5.7.1 Nonsteroidal anti-inflammatory drugs (including COX-1 or COX-2 inhibitors)

Patients who are regularly taking NSAIDs (including cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase 2 (COX-2) inhibitors) at Screening are allowed to continue the specific treatment in accordance to the posology and method of administration as described in the local SmPC.

Patients must refrain from any NSAID intake during at least 24 hours before a visit involving a disease activity assessment.

The dose of NSAID(s) taken during the study must be recorded on the corresponding eCRF page. More guidance on NSAIDs can be found in Appendix 10.

5.5.7.2 Analgesics other than NSAIDs

Patients may take paracetamol/acetaminophen at doses of ≤ 500 mg per day. Patients must refrain from any paracetamol/acetaminophen intake during at least 24 hours before a study visit involving a disease activity assessment.

5.5.7.3 Methotrexate

Patients who are taking MTX (≤ 25 mg/week) at Screening should be on a stable dose for at least 4 weeks before randomization to be eligible for inclusion in the study and apply folic acid supplement to avoid toxic effects.

Patients are required to remain on a stable dose of MTX (≤ 25 mg/week) along with a folic acid supplement from Baseline until Week 8. The dose may be decreased only due to toxicity. After Week 8, it is recommended that the patient continues on the same stable dose of MTX until Week 24. The folic acid supplement should be continued throughout the study irrespective of the dose of MTX.

Stable folic acid supplementation is required latest at randomization in order to minimize the likelihood of MTX-associated toxicity.

The dose of MTX taken during the study must be recorded on the corresponding eCRF page.

5.5.7.4 Sulfasalazine

Patients taking sulfasalazine (≤ 3 g/day) at Screening should be on a stable dose for at least 4 weeks before randomization to be eligible for inclusion in the study.

Patients are required to remain on a stable dose of sulfasalazine (≤ 3 g/day) from Baseline until Week 8. After Week 8, it is recommended that the patient continues on the same stable dose of sulfasalazine until Week 24.

The dose of sulfasalazine taken during the study must be recorded on the corresponding eCRF page.

5.5.7.5 Corticosteroids

Patients who received any intramuscular, intra-articular or intravenous corticosteroid within 4 weeks prior to randomization are NOT eligible to enter this study. Patients who are taking systemic corticosteroids at Screening should be on a stable dose ≤ 10 mg/day of prednisone or equivalent (see Table 5-1) for at least 2 weeks before randomization to be eligible for inclusion in the study.

Patients are required to remain on a stable dose of systemic corticosteroids up to a maximum daily dosage of 10 mg prednisone equivalent from Baseline until Week 8. After Week 8, it is recommended that the patient continues on the same stable dose of corticosteroids until Week 24.

The dose of systemic corticosteroids during the study must be recorded on the corresponding eCRF page.

Table 5-1 Corticosteroids conversion table for the equivalence of 1 mg of cortisone

Corticosteroid	Equivalence of 1 mg of cortisone
Cortisone	1 mg
Prednisone, prednisolone	0.2 mg
Methylprednisone, triamcinolone	0.16 mg
Dexamethasone	0.03 mg
Fludrocortisone	0.08 mg
Deflazacort	0.24 mg
Paramethasone	0.08 mg
Hydrocortisone, cortisol	0.8 mg

Sources: Asare 2007, Colburn 2012, Grover et al 2007, Liu et al 2013, Saviola et al 2007, Shaikh et al 2012.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is not allowed after the start of the wash-out period unless otherwise specified below.

Patients who have previously been on a TNFα inhibitor will be allowed entry into the study after an appropriate wash-out period prior to randomization (see Table 5-2):

- 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route)
- 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion)
- 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route)
- 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days (s.c. route)
- 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days (s.c. route)

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

Table 5-2 Prohibited medication

Medication	Washout period (before randomization)
Etanercept*	4 weeks
Infliximab*	8 weeks
Adalimumab*	10 weeks
Golimumab*	10 weeks
Certolizumab*	10 weeks
Unstable dose of MTX or sulfasalazine	4 weeks
Conventional synthetic DMARDs other than MTX or sulfasalazine	4 weeks
Leflunomide	8 weeks
Leflunomide with cholestyramine wash-out	4 weeks
Targeted synthetic DMARDs (e.g. apremilast)	4 weeks
Systemic corticosteroids > 10 mg prednisone equivalent**	2 weeks
Intramuscular, intra-articular or intravenous corticosteroid treatment	4 weeks
Any biological immunomodulating agents, except those targeting TNFα*	No prior exposure
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents (e.g. Campath®, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	No prior exposure
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Analgesics other than NSAIDs or low strength opioids PRN, tramadol (refer to Section 5.5.7.2 for allowed doses of analgesics other than NSAIDs)	4 weeks
High strength opioids	4 weeks
Live vaccinations	6 weeks

CD=cluster of differentiation, COX1=cyclo-oxygenase 1, COX2=cyclo-oxygenase 1, DMARDs=disease-modifying anti-rheumatic drugs, MTX=methotrexate, NSAIDs=non-steroidal anti-inflammatory drugs, PRN=pro re nata (as needed), TNFα=tumor necrosis factor alpha

* These agents fall under the category of biologic immunomodulators and are prohibited medications; administration of these agents requires study treatment discontinuation (see Section 5.6.2)

** See details about corticosteroid management in Section 5.5.7.5

5.5.9 Emergency breaking of assigned treatment code

Emergency breaking of an assigned treatment code must only be undertaken when it is essential in order to treat a patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide the protocol number (CAIN457H3301), the study drug name (if available), the Patient Number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the patient in case an emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding.

5.6 Study completion and discontinuation

5.6.1 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. Visit 10/Week 24 (see Table 6-1). 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. In any case, the investigator or site staff must contact the IRT as soon as possible to record the patient's study completion and/or discontinuation.

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 a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

5.6.2 Discontinuation of study treatment

Discontinuation of study 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. If discontinuation occurs for any reason in a treatment period (i.e. Treatment Period 1 or 2), the investigator/qualified site staff must make every effort to determine the primary reason for the patient's discontinuation from the study. This information will then be recorded by the investigator/qualified site staff in the applicable eCRF section.

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 AEs:
  a. Any severe AE or SAE that is not compatible with administration of study medication, including AEs that require treatment with prohibited co-medication
  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 non--invasive malignant colon polyps, which are being or have been removed

c. Life-threatening infection
d. Severe hypersensitivity reaction or anaphylactic reaction
e. 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 (general guidance on clinically notable laboratory values is provided in Appendix 1)
f. Pregnancy
g. Use of any biologic immunomodulating agent except secukinumab

For patients who discontinue study treatment the CRF should be completed, giving the date and primary reason for stopping study treatment.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because the treatment code has been broken, please refer to Section 5.5.9.

Efficacy and safety will be assessed in detail at every study visit, and patients who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Patients who prematurely discontinue the study should return and complete assessments associated with the Week 24 visit (4 weeks after the last study treatment, see Table 6-1) and any AEs that are treatment emergent should be reported until 12 weeks after the last study treatment. The final visit should be performed before any new treatment is initiated.

Patients who prematurely withdraw from the study will not be replaced.

5.6.3 Withdrawal of informed consent

Withdrawal of consent occurs only when a patient does not want to participate in the study any longer and does not want any further visits or assessments, does not want any further study related contacts and does not allow analysis of already obtained biological material.

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used.

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 (Table 6-1).

5.6.4 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 formally considered lost to follow-up until his/her scheduled end of study visit has passed.

5.6.5 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 for participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible 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 will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. During the study, the assessments must be performed as indicated in Table 6-1.

Patients must be seen for all visits on the designated day, or as close to it as possible to the original planned visit.

- For visits scheduled through Week 4, the study treatment should not be administered less than 3 days after the previous administration.
- For visits scheduled after Week 4, the study treatment should not be administered less than 14 days after the previous administration.

Note: Missed or rescheduled visits should not lead to automatic discontinuation of patients.

Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the AEs and concomitant medications reconciled on the CRF. If patients refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Documentation of attempts to contact the patient should be recorded in the source documentation.

No study assessment will be performed unless patients sign the ICF. Once a patient signs the ICF, he/she will be screened for eligibility criteria. The Screening Period will be flexible in terms of the time required to washout prior anti-rheumatic and other medications and will have a recommended duration of up to 10 weeks. During the Screening Visit, assessments will be performed as outlined in Table 6-1. Patients who have screen-failed once may be re-screened once if, in the opinion of the investigator, the risk/benefit ratio for the patient is positive and it is likely that the patient can meet all eligibility criteria at the second screening

time point. In this case, the patient will receive a new Patient Number (new Informed Consent process, separate IRT entry and eCRF data set applies).

The duration of the washout period will be determined at the Screening Visit. Note: All patients evaluated at Screening (Visit 1) for eligibility should not be screen failed based on a medication requiring washout, unless the patient will be unable to complete the washout in the appropriate time frame before randomization.

Patients should be seen for all visits to perform the scheduled assessments on the designated day, or as close to is as possible, i.e. not exceeding the recommended visit window outlined in Table 6-1 and Table 6-2.

Table 6-1 Assessment schedule

	Screening	Treatment Period 1 Double-blind placebo-controlled (last dose at Week 4)					Treatment Period 2 Double-blind active (last dose at Week 20)				USV**	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EOS/ PPD***		* EOS/PPD - Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 24 visit (i.e. 4 weeks after the last study treatment). ** Unscheduled visit – assessments at the discretion of the investigator.
Week	**−10 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**20**	**24**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**		
Information and informed consent	X											
Inclusion & exclusion criteria	X	X										
axSpA history		X										
Spinal pain responder assessment							X					
Demographics	X											
Relevant medical history/ current medical conditions	X											
Prior medication/ concomitant medication	X	X	X	X	X	X	X	X	X	X	X	
AEs/ SAEs (including injection site reactions)	X	X	X	X	X	X	X	X	X	X	X	AEs/SAEs occurring after the patient has signed the informed consent (including those that occur during home administration of study drug) must be captured on the appropriate eCRF page. Any AEs that are treatment-emergent should be reported until 12 weeks after the last study treatment.

[redacted]

	Screening	Treatment Period 1 Double-blind placebo-controlled (last dose at Week 4)					Treatment Period 2 Double-blind active (last dose at Week 20)				USV**	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EOS/ PPD***		* EOS/PPD - Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 24 visit (i.e. 4 weeks after the last study treatment). ** Unscheduled visit – assessments at the discretion of the investigator.
Week	**−10 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**20**	**24**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**		
Smoking history		X										
Cardiovascular medical history	X											
Physical examination	S	S	S	S	S	S	S	S	S	S	S	
Height† and weight		X								X	X	† Height will be assessed at Visit 2 or unscheduled visit only.
Vital signs	X	X	X	X	X	X	X	X	X	X	X	
QuantiFERON TB-Gold test	X										X	
Chest X-ray or MRI (for study eligibility)	X										X	A chest X-ray or MRI is required if it was not performed and evaluated within 3 months before Screening. The X-ray should be performed after it is certain the patient meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. In some sites selected, the X-ray may be replaced by a chest MRI assessment.
Electrocardiogram	X										X	
Hematology	X	X				X	X	X		X	X	

	Screening	Treatment Period 1 Double-blind placebo-controlled (last dose at Week 4)					Treatment Period 2 Double-blind active (last dose at Week 20)				USV**	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EOS/ PPD***		* EOS/PPD - Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 24 visit (i.e. 4 weeks after the last study treatment). ** Unscheduled visit – assessments at the discretion of the investigator.
Week	**−10 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**20**	**24**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**		
Blood chemistry	X	X				X	X	X		X	X	Blood sample to be collected with patient in fasting state.
HLA-B27 [redacted]	X											
High sensitivity C-reactive protein	X	X					X			X	X	Results should be blinded in the laboratory report after Visit 2.
Urinalysis	X	X				X	X	X		X	X	Urine dipstick test to be performed at site. Test supply will be provided by central laboratory.
Serum pregnancy test	X										X	
Urine pregnancy test		X				X	X	X		X	X	Test to be performed at site. Test supply will be provided by central laboratory.
Hepatitis B, C or HIV serology (only in countries where required)	S											Hepatitis B and/or hepatitis C and/or HIV serology testing to be performed during Screening period only if required as per local medical practice or local regulations prior to initiation of therapy.

	Screening	Treatment Period 1 Double-blind placebo-controlled (last dose at Week 4)					Treatment Period 2 Double-blind active (last dose at Week 20)				USV**	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EOS/ PPD***		* EOS/PPD - Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 24 visit (i.e. 4 weeks after the last study treatment). ** Unscheduled visit – assessments at the discretion of the investigator.
Week	**−10 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**20**	**24**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**		
												These assessments will be documented in source records only and will not be entered into the eCRF.
Randomization via IRT		X					X†					† At Visit 8, non-responders and patients receiving placebo will be re-randomized to secukinumab 150 mg or 300 mg
IRT contact such as for registration or drug supply including home administration	X	X	X	X	X	X	X	X	X	X		
Administration of study treatment		X	X	X	X	X	X	X	X			Patients will be required to self-administer secukinumab at home at Week 16. Please refer to Table 6-2 for timing of home administration.
Check self-administration log for home administration									S			At Visit 9, patients must return the self-administration log along with all dispensed PFS and drug packaging

	Screening	Treatment Period 1 Double-blind placebo-controlled (last dose at Week 4)					Treatment Period 2 Double-blind active (last dose at Week 20)				USV**	Comments
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10 EOS/ PPD***		* EOS/PPD - Patients who prematurely discontinue during the treatment period should return for assessments associated with the Week 24 visit (i.e. 4 weeks after the last study treatment). ** Unscheduled visit – assessments at the discretion of the investigator.
Week	**−10 to -1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**20**	**24**		
Recommended visit window (days)			**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 5**	**± 5**	**± 5**		
Spinal pain assessment on NRS	X	X	X	X	X	X	X	X	X	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	
PASS		X	X	X	X	X	X	X	X	X	X	
Patient global assessment of disease activity		X					X			X	X	
FACIT-Fatigue©		X					X			X	X	
ASAS Health Index		X					X			X	X	
Treatment completion form										X		

AE=adverse event, ASAS=Assessment of Spondyloarthritis International Society, axSpA=axial spondyloarthritis, BASDAI=Bath ankylosing spondylitis disease activity index, BSL=baseline, eCRF=electronic case report form, EOS=end of study,

FACIT-Fatigue©=functional assessment of chronic illness therapy-fatigue, HIV=human immunodeficiency virus, HLA-B27=Human Leukocyte Antigen-B27, IRT=interactive response technology, MRI=magnetic resonance imaging, NRS=numerical rating scale, PASS=Patient Accepted Symptoms State, PFS=prefilled syringe, PPD=Premature patient withdrawal, SAE=Serious adverse event, SCR=screening, TB=tuberculosis, USV=unscheduled visit

X=assessment to be recorded on clinical database, S=assessment to be recorded on source documentation only

An overview of study drug administration for Treatment Period 2 is presented in Table 6-2.

Table 6-2 Overview of study drug administration for Treatment Period 2

Study visit	**7**	**8**		**9**
Week	**8**	**12**	**16**	**20**
Recommended visit windows (days)	± 2	± 5	± 5	± 5
Study drug administration (all groups)	S	S	H	S

H=home; S=study center

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion page for the Screening period, demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. Information on withdrawal of consent must be completed if consent has been withdrawn during the Screening period. The Death eCRF should be completed in the case of death during the Screening period.

All patients who provide signed informed consent but discontinue prior to first intake of study drug on Day 1 (Baseline Visit) are considered to be screen failures. If a patient discontinues prior to or at Day 1, the reason for screen failure will be entered on the appropriate eCRF page. For details on completing the eCRF please refer to the CRF completion guideline.

For all patients who sign the informed consent and enter into the next period of the study, all AEs occurring after the informed consent is signed will be recorded on the AE eCRF page.

6.2 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 6-1).

6.2.1 Demographic data

Patient demographic data to be collected for all patients include: date/year of birth (as allowed per local regulation), sex, race, ethnicity, height, weight, child-bearing potential (for females only), and source of patient referral.

6.2.2 Baseline characteristics

6.2.2.1 AxSpA history

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

- Date of first diagnosis of axSpA prior to the Baseline Visit (by a rheumatologist)
- Date of first signs and symptoms of axSpA including date of onset of IBP
- AS diagnosis including X-ray with presence/absence of sacroiliitis

- nr-axSpA diagnosis by MRI or by presence of HLA-B27
- Positive SpA features (Appendix 4)
- Previous treatments of axSpA and the reason for discontinuation of these treatments

Diagnosis of axSpA (either AS or nr-axSpA) should have been in accordance with ASAS axSpA criteria (Appendix 4 and Appendix 5) as defined in the inclusion criteria (Section 4.1).

6.2.2.2 Smoking history

The current and/or previous use of tobacco products including e-cigarettes will be recorded, as well as the approximate consumption per year. Non-smokers will be advised not to start smoking during the study.

6.2.2.3 Co-morbidities – cardiovascular medical history

Any information pertaining to cardiovascular medical history assessed prior to Screening should be reported as cardiovascular history in the eCRF. Cardiovascular risk factors should also be recorded.

6.2.2.4 Relevant medical history/current medical conditions

Relevant medical history and current medical conditions (not including axSpA) present prior to signing the ICF will be recorded in the medical history eCRF. 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.

6.2.2.5 Prior medication/concomitant medication

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.

6.2.2.6 Chest X-ray

If patients do not have a chest X-ray obtained within 3 months preceding the Screening Visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the patient meets all inclusion/exclusion criteria. In some sites selected by Novartis, the X-ray assessment may be replaced by a MRI assessment.

6.2.2.7 Tuberculosis status

A QuantiFERON TB-Gold test is to be performed at Screening and the results must be available prior to randomization to determine the patient's eligibility. The test will be used to screen the patient population for latent TB infection. 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, or if presence of latent TB is established then treatment according to local guidelines must have been initiated.

The 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.

6.2.2.8 HLA-B27

A blood sample will be obtained from all patients to analyze HLA-B27, [redacted].

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

6.2.2.9 Hepatitis B, C and HIV serology

Hepatitis B, C and HIV serology can be performed at Screening if required as per local medical practice or local regulations prior to initiation of biological therapy in order to rule out the presence of Hepatitis B, C or HIV infection.

6.2.3 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed as indicated in Table 6-1. The investigator/qualified site staff must review and initial the tracing. The tracing must then be stored with the patient's source documents. If the ECG findings are clinically relevant and would prevent the patient from participating in the study (taking into account the patient's overall status as well as the medication profile), the patient should be recorded as a screen failure, should NOT be enrolled and should not receive treatment. Any clinically relevant finding should be reported as medical history.

6.2.4 Other baseline characteristics

Other baseline characteristic data to be collected for all patients (all laboratory tests are performed centrally except where indicated; see also Table 6-1) include the following:

- Vital signs, hematology, clinical chemistry and urine laboratory tests, and physical examination. Height and weight will also be assessed. For women of childbearing potential, a serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at Baseline.
- Baseline assessments of spinal pain (NRS), BASDAI, patient's global assessment of disease activity, PASS, ASAS health index, FACIT-Fatigue©, and hsCRP assessment as described in Section 6.4.

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

All doses and dates of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Compliance will also 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.

6.4 Efficacy

Efficacy will be evaluated using the following assessments:

- Spinal pain NRS
- BASDAI
- ASDAS
- FACIT-Fatigue©
- PASS
- ASAS Health Index

All of the above listed efficacy assessments are PROs except for ASDAS.

All questionnaires should be completed at the scheduled study visit prior to the patient seeing the investigator for any other clinical assessment or evaluation. The patient should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check each questionnaire for completeness and encourage the patient to complete any missing responses. Investigators should not encourage the patients to change the responses reported in the completed questionnaires. Guidelines for administering the PRO questionnaires can be found in Appendix 9.

Completed questionnaires should 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 7 of the protocol.

All questionnaires are available, where possible, in the local languages of the participating countries. PRO questionnaires will be administered as defined in the schedule of assessments (see Table 6-1).

6.4.1 Numerical rating scale spinal pain assessment

The spinal pain NRS assessment is an 11-point scale to assess pain intensity in patients who are able to self-report. The patient should answer 2 questions in order to make 2 pain ratings (point a number on NRS between 0 and 10), corresponding to the intensity of spinal pain experienced on an average during the previous week; the average of the 2 ratings is to be used to represent the patient's level of pain (see Appendix 7).

6.4.2 Bath ankylosing spondylitis disease activity index (BASDAI)

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

- Fatigue/tiredness
- Spinal pain (neck, back or hip pain)

- Pain/swelling in joints (other than neck, back, hips)
- Enthesitis, or inflammation of tendons and ligaments (areas of localized tenderness)
- Morning stiffness duration and severity

The purpose of BASDAI in this study is to assess pain, discomfort and fatigue in patients with axSpA. BASDAI was originally validated to measure disease status and symptoms in patients with AS; however, one study (Rudwaleit et al 2009b) demonstrated that the level of disease activity as measured by the BASDAI, morning stiffness, fatigue, and pain at night is highly comparable between patients with AS and those with nr-axSpA.

Please see Appendix 8 for more details.

6.4.3 Ankylosing spondylitis disease activity score

The ASDAS is a composite index to assess disease activity in AS (Sieper 2009, Lukas 2009).

The ASDAS-CRP will be used to assess the disease activity status. Parameters used for the ASDAS include:

- Spinal pain (BASDAI question 2) (Section 6.4.2)
- Patient's global assessment of disease activity (Section 6.4.3.1)
- Peripheral pain/swelling (BASDAI question 3) (Section 6.4.2)
- Duration of morning stiffness (BASDAI question 6) (Section 6.4.2)
- hsCRP in mg/L (Section 6.4.3.2)

Disease activity states are defined as follows: inactive disease, moderate disease activity, high disease activity, and very high disease activity. The 3 values selected to separate these states are < 1.3 between inactive disease and moderate disease activity, < 2.1 between moderate disease activity and high disease activity, and > 3.5 between high disease activity and very high disease activity. Selected cut-offs for improvement scores are a change ≥ 1.1 unit for "minimal clinically important improvement" and a change ≥ 2.0 units for "major improvement" (Machado 2011).

6.4.3.1 Patient's global assessment of disease activity

The patient's global assessment of AS disease activity will be performed using a NRS ranging from 0 (not active) to 10 (very active) (Sieper et al 2009) based on the following question:

How active was your disease on average during the last week?

6.4.3.2 High sensitivity C-reactive protein

A central laboratory will be used for analysis of hsCRP. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Laboratory Manual. Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment. Since the results of this test may unblind study personnel, results from the central laboratory will be provided for Screening and Baseline only. The hsCRP results from samples collected during the treatment periods will be revealed following the database lock only.

6.4.4 Functional assessment of chronic illness therapy-fatigue

The 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 patient should complete all items.

The purpose of FACIT-Fatigue© in this study is to assess the impact of fatigue on patients with axSpA.

6.4.5 Patient acceptable symptoms state

The PASS has been defined as the highest level of symptoms beyond which patients consider themselves well. Measurement of patient well-being also enables evaluation of how soon and for how long the patient feels good (Maksymovych et al, 2010).

During the PASS assessment, the patient will answer the following question:

- Considering all the different ways your disease is affecting you, if you would stay in this state for the next months, do you consider that your current state is satisfactory?

The purpose of PASS in this study is to assess the well-being of patients with axSpA. Achievement of PASS indicates that the patient feels well.

6.4.6 ASAS Health Index

The ASAS health index is a disease-specific questionnaire that was developed based on the comprehensive international classification of functioning, disability and health (ICF) Core Set for AS (Kiltz et al 2014). The ASAS health index 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 6-3.

Table 6-3 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	Economic self-sufficiency	d870

Item	Categories	ICF number
my rheumatic disease.		
I sleep badly at night	Sleep	b134
I cannot overcome my difficulties.	Handling stress	d240

Source: Kiltz et al 2014

6.4.7 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are standard measures used across AS and nr-axSpA trials.

6.5 Safety

- Physical examination
- Vital signs
- Laboratory evaluations
- Pregnancy and assessment of fertility

6.5.1 Physical examination

Physical examinations, which will be performed as defined in Table 6-1, will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF that meet the definition of an AE must be recorded in the AE eCRF and if SAE criteria are met, findings must also be reported as a SAE.

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed after the patient has been sitting for 5 minutes, with back supported and both feet placed on the floor. Sites should use a validated device with an appropriately sized cuff and each blood pressure measurement will be recorded in the source (Mancia et al 2007). In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If possible, assessments should be performed by the same study site staff member throughout the study.

Systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes).

Normal blood pressure will be defined as a systolic pressure of 90 to < 120 mmHg, and a diastolic blood pressure of 60 to < 80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure of < 90 mmHg and/or a diastolic blood pressure of < 60 mmHg). A blood pressure indicative of

prehypertension (systolic blood pressure of 120 to < 140 mmHg and/or diastolic blood pressure of 80 to < 90 mmHg) will not be regarded as notable (Chobanian et al 2003).

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm) under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

Whether action needs to be taken to address notable vital signs will be decided by the investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

6.5.3 Height and body weight

Height in cm and body weight (to the nearest 0.1 kg in indoor clothing) (both without shoes) will be measured as indicated in Table 6-1. If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected as listed below and outlined in the schedule of assessments (see Table 6-1). Urinalysis and urine pregnancy tests will be performed on site with supplies provided by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators 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.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST/SGOT, ALT/SGPT, gamma-glutamyl transferase (γGT), alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin, and uric acid.

6.5.4.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The measurements for standard parameters such as protein, glucose, blood and WBCs will be performed and results recorded in the appropriate eCRF page.

6.5.5 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 6-1. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

In the case of oophorectomy alone, the woman is considered not of childbearing potential only when her reproductive status has been confirmed by follow-up hormone level assessment.

6.5.6 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in axSpA. A chest X-ray at Screening (or within 3 months prior to Screening) is performed to rule out the presence of a pulmonary malignancy of infectious process in particular TB.

The radiation exposure that results from these safety measurements are estimated to be far below 1 mS. For effective radiation doses under 3 mS (300 mrem), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

6.6 Other assessments

No additional tests will be performed on patients entered into this study.

7 Safety monitoring

7.1 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 after providing written informed consent for participation in the study until the end of study visit. 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 product are also considered an AE irrespective if a clinical event has occurred.

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

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 underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

AEs must be recorded in the AE eCRF under the signs, symptoms or diagnosis associated with them. Medical conditions/diseases present before starting study treatment will only be considered AEs if they worsen after starting study treatment (any procedures specified in the protocol).

As far as possible, each AE should be described by (but not limited to) the following information:

- 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
- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- whether it constitutes an SAE (see Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study 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 Investigator Notification (IN). New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new AE (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. Any AEs that are treatment emergent should be reported until 12 weeks after last study treatment. This information must be recorded in the

investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of serious adverse event

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:

- is fatal or life-threatening
- 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 listed above e.g. may require 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

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

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).

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).

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

7.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 12 weeks after last administered dose of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after this should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

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 (either initial or follow-up) is collected and recorded on the SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship 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 after awareness of the SAE to the local Novartis Drug Safety and Epidemiology (DS&E) Department.. 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. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation. 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.

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 DS&E 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 (SUSARs) 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.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following 2 categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter

- Liver events, which will require close observation, follow-up monitoring and completion of the standard base Liver CRF pages

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personnel at the trial site as summarized below (please see Appendix 2 for detailed information).

For the liver laboratory trigger:

- Repeating the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event, which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist consultancies, based on the investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

The following 2 categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to Baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 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 dose administration record 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.

See Table 7-1 for guidance on capturing the study treatment errors including misuse/abuse.

Table 7-1 Treatment error types

Treatment error type	Document in DAR eCRF (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

AE=adverse event, eCRF=electronic case report form, DAR=dose administration record, SAE=serious adverse event

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis/CRO 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.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis DS&E Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (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 Clinical Research Associate organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis 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, ECGs, 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 informed consent form 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 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.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs using fully validated software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or the CRO working on behalf of Novartis reviews the data entered into the CRFs by investigational staff for completeness and accuracy and instructs the site personnel to make any required corrections or additions. Queries are sent to the investigational site using

an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or the CRO working on behalf of Novartis that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally (if indicated as centrally measured as per Table 6-1) and the results will be sent electronically to Novartis (or a designated CRO).

Electrocardiogram readings will be collected locally and the results will be reported in the CRF to Novartis (or a designated CRO) or, in case of site lacking equipment, may be collected and processed centrally and reported electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an IRT.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

8.4 Data monitoring committee

Not required.

8.5 Adjudication committee

Not required.

9 Data analysis

Data analysis will be conducted on all patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. For all details please refer to the Statistical Analysis Plan.

9.1 Analysis sets

The following analysis sets will be used in this study:

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

The **Randomized Set** will consist of all patients who were randomized into this study at Baseline.

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

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

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

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

9.2 Patient demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristics for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and for all patients.

9.3 Treatments

9.3.1 Study treatment

The analysis of study treatment data will be based on the Safety Set.

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

9.3.2 Prior and concomitant treatment

Prior and concomitant treatments and non-drug therapies will be summarized by treatment group in separate tables.

Prior treatments are defined as treatments taken and stopped prior to the first dose of study treatment. Any treatment given at least once between the day of first dose of randomized study treatment and the last study visit day will be a concomitant treatment, including those that were started pre-baseline and continued into the treatment period.

Treatments will be presented in alphabetical order, by anatomical therapeutic classification (ATC) codes and grouped by anatomical main group. The overall number and percentage of

patients receiving at least 1 treatment in a particular ATC will also be presented in summary tables.

9.4 Analysis of the primary variable

9.4.1 Primary variable

The primary endpoint is the proportion of patients with a spinal pain NRS score < 4 at Week 8. This is referred to as 'response' below.

9.4.2 Statistical model, hypothesis, and method of analysis

The null hypothesis to be rejected is that the odds of response at Week 8 are equal in both treatment groups. The corresponding alternative hypothesis is that the odds of response at Week 24 are higher under secukinumab compared to placebo.

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

- 0 corresponds to placebo
- 1 corresponds to secukinumab

The following hypotheses will be tested:

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

In other words:

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

The primary analysis will be performed comparing treatments with respect to the primary efficacy variable in a logistic regression model with the factors treatment, country and the 2 stratification factors (prior exposure to TNF inhibitors and naïve/ inadequate responders to TNFα inhibitors). The odds ratio and its 95% confidence interval (CI) and 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; however, superiority of secukinumab will be claimed only if the direction is correct, i.e. if the odds of response are larger under secukinumab.

9.4.3 Handling of missing values/censoring/discontinuations

For the primary endpoint, patients with missing assessments at Week 8 will be considered as non-responders.

9.4.4 Sensitivity analyses

The raw spinal pain NRS scores will be analyzed using a repeated measures analysis of variance (ANOVA) model. The model will include the same factors as the logistic model above plus the baseline score as a covariate.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary endpoint, the proportion of patients with a BASDAI score < 4 at Week 8, will be analyzed analogous to the primary endpoint. The secondary endpoint will be included in a confirmatory testing strategy, it will be tested hierarchically after the primary endpoint. Confirmatory evidence for the superiority of secukinumab with respect to the secondary endpoint will be claimed only if the 2-sided p-value from the logistic regression model for the factor "treatment" is < 0.05 and if the direction is correct, i.e. if the odds of response are larger under secukinumab and if the superiority of secukinumab with respect to the primary endpoint has already been demonstrated.

9.5.2 Safety variables

9.5.2.1 Adverse events

Treatment emergent AEs (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized.

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 (SOC) and having each individual AE (preferred term (PT)). Adverse events will also be summarized by severity and relationship to study treatment. If a patient reported more than 1 AE with the same PT, the AE with the greatest severity will be presented. If a patient reported more than 1 AE within the same primary SOC, the patient will be counted only once with the greatest severity at the SOC level, where applicable. Serious adverse events will also be summarized.

These summaries may be presented separately by study periods, i.e. Treatment period 1 (from Baseline to time of study drug administration at Week 8) and Treatment Period 2 (from dosing at Week 8 to Week 24).

Separate summaries will be provided for any deaths, SAEs, other significant AEs such as AEs leading to discontinuation and AEs leading to dose adjustment (including study treatment discontinuation).

9.5.2.2 Laboratory data

Laboratory evaluations will be summarized for 3 groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from Baseline in laboratory data at each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from Baseline will only be summarized for patients with both Baseline and post-Baseline assessments. For each parameter, the maximum change from Baseline within each study period will also be analyzed.

9.5.2.3 Vital signs

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 a Baseline and post-Baseline value.

9.6 Analysis of exploratory variables

All endpoints relating to exploratory objectives will be summarized descriptively. Summary statistics will include relative and absolute frequencies for the categorical variables and the number of patients, minimum, mean, median and maximum for continuous variables. Time courses of response rates and mean NRS-scores will be displayed graphically. Inferential statistical test may be calculated as appropriate, they will use the same methodology as described for the primary endpoint. Details will be specified in the Statistical Analysis Plan.

9.7 Interim analyses

No interim analysis is planned for this study.

9.8 Sample size calculation

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

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

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after

such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, 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 assent by personally signing and dating the written informed consent document or a separate assent form. 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 a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of childbearing 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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional IRB/IEC approval will be obtained.

10.3 Responsibilities of the investigator and institutional review board/independent ethics committee

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, 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.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality control and quality assurance

Novartis maintains a robust Quality Management system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities,

the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group 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 processes, and are performed according to written Novartis processes.

11 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 is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

11.1 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 intended to eliminate an apparent immediate hazard to patients 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, the reporting requirements identified in Section 7 (Safety monitoring) must be followed.

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values

The following criteria included in Table 13-1 will be used to define expanded limits and notable abnormalities of key laboratory tests.

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

Table 13-1 Safety analyses: expanded limits and notable criteria

Laboratory variable	Final harmonization	
	Notable criteria	
	Standard units	SI units
Liver function and related variables		
AST/SGOT	> 3 x ULN	> 3 x ULN
ALT/SGPT	> 3 x ULN	> 3 x ULN
Bilirubin	> 2 x ULN	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN	> 2.5 x ULN
Renal function and related variables		
Creatinine (serum)	> 2 x ULN	> 2 x ULN
Hematology variables		
Hemoglobin	20 g/L decrease from Baseline	
Platelet count	< 100 x $10E^9$/L	
White blood cell count	< 0.8 x LLN	
Neutrophils	< 0.9 x LLN	

ALT/SGPT=alanine aminotransferase/serum glutamic pyruvic transaminase, AST/SGOT=aspartate aminotransferase/serum glutamic oxaloacetic transaminase, LLN=lower limit of normal, ULN=upper limit of normal

13.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 13-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
Liver events	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
ALT=alanine aminotransferase, ALP=alkaline phosphatase, AST=aspartate aminotransferase, INR=international normalized ratio, TBL=total bilirubin, UNL=upper normal limit

Table 13-3 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Alb=albumin, AESI=adverse event of special interest, ALP=alkaline phosphatase, CRF=case report form, INR=international normalized ratio, γGT=gamma glutamyl transferase, LFT=liver function test, PT=prothrombin time, TBL=total bilirubin, ULN= upper limit normal

13.3 Appendix 3: Specific renal alert criteria and actions

Table 13-4 Specific renal alert criteria and actions

Serum event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: serum creatinine within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: serum creatinine level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	

13.4 Appendix 4: 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

- IBP
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn's disease or colitis
- Good response to NSAIDs
- Family history for SpA
- HLA-B27
- Elevated C-Reactive Protein

13.5 Appendix 5: 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.

13.6 Appendix 6: 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)

13.7 Appendix 7: Spinal pain numerical rating scale

The spinal pain NRS is an 11-point scale to assess pain intensity in patients who are able to self-report. The patient is asked to answer 2 questions in order to make 2 pain ratings (point a number on NRS between 0 and 10), corresponding to the intensity of spinal pain experienced on an average during the previous week; the average of the 2 ratings is to be used to represent the patient's level of pain.

Nocturnal back pain

Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?

NRS scale 0 to 10, no pain to unbearable pain

Total back pain

Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?

NRS scale 0 to 10, no pain to unbearable pain

13.8 Appendix 8: 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 numerical rating scale), 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 2 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 patients with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete).

13.9 Appendix 9: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

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

Before completion

1. Patients should be provided with the correct questionnaire at the appropriate visits and in the appropriate language
2. Patients 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 (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)
2. Check for multiple responses that were made in error

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. Any person other than the designated study coordinator should provide no help to the patient. 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 that 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 using an electronic device. 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 electronic device 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.

13.10 Appendix 10: ASAS recommendations for collecting, analyzing and reporting NSAID intake

Table 13-5 ASAD-NSAID equivalent score

NSAID	Dose comparable to 150 mg diclofenac	Maximum dose used in AS	Consensus
Diclofenac	/	n=60* 150 (150-200)	150
Naproxen	n=57 1000 (1000-1000)	n=59 1000 (1000-1500)	n=47/50† 1000
Aceclofenac	n=15 200 (200-200)	n=14 200 (200-200)	n=29/29 200
Celecoxib	n=61 400 (300-400)	n=60 400 (400-400)	n=47/50 400
Etodolac	n=15 600 (400-800)	n=13 600 (600-600)	n=17/20 600
Etoricoxib	n=36 90 (90-90)	n=37 120 (90-120)	n=42/46 90
Flurbiprofen	n=13 200 (200-300)	n=13 300 (200-300)	n=15/18 200
Ibuprofen	n=54 2400 (1600-2400)	n=54 2400 (2400-2400)	n=39/45 2400
Indometacin	n=57 150 (100-150)	n=58 150 (150-200)	n=42/47 150
Ketoprofen	n=26 200 (200-200)	n=25 200 (200-300)	n=21/23 200
Meloxicam	n=58 15 (15-15)	n=55 15 (15-22.5)	n=42/48 15
Nimesulide	n=8 200 (200-200)	n=9 200 (200-200)	n=16/16 200
Phenylbutazone	n=28 400 (200-500)	n=28 400 (250-600)	n=25/28 400
Piroxicam	n=51 20 (20-20)	n=50 20 (20-40)	n=46/46 20
Tenoxicam	n=17 20 (20-20)	n=16 25 (20-40)	n=18/18 20

Source: Dougados et al 2011
Results of the survey evaluating the opinion of ASAS members about the comparable efficacy of each NSAID with 150 mg of diclofenac.
Values given are:
*first row, n-number of ASAS members giving an answer to the question;
second row, median dose in mg (tertiles)
† first row, n=number of ASAS members who have voted in favour of such a dose/the total number of ASAS members who have voted; second row, agreed dose.
AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis International Society; NSAID, non-steroidal anti-inflammatory drug