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AIN457

Clinical Trial Protocol CAIN457P12301 / NCT04156620

A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis or non-radiographic axial SpondyloArthritis

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate aminotransferase
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
[redacted]	[redacted]
BDR	Bioanalytical Data Report
BMI	Body Mass Index
BSL	Baseline
BUN	blood urea nitrogen
C_{avg}	Average concentration
CFR	Code of Federal Regulation
CK	creatine kinase
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CO	Country Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
cs-DMARD	conventional synthetic Disease Modifying Anti-rheumatic Drug
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
C_{trough}	trough concentration
CTT	Clinical Trial Team
DILI	Drug-Induced Liver Injury
DMARD	Disease Modifying Anti-rheumatic Drug
[redacted]	[redacted]
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture

eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medical Agency
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	gamma glutamyl transferase
h	hour
HDL	High Density Lipoprotein
HIV	human immunodeficiency virus
HLA	Human Leukocyte Antigen
HRQoL	Health-related quality of life
hsCRP	high sensitivity C-Reactive Protein
HSV	Herpes Simplex Virus
i.v.	intravenous
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDL	Low Density Lipoprotein
LFT	Liver function test
LiV	Liquid in Vial
LLN	lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
MAR	Missing at random
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
mL	milliliter(s)

MMRM	Mixed effect Model for Repeated Measurements
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
nr-axSpA	non-radiographic axial spondyloArthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
NY	New York
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	Purified Protein Derivative
PRN	as needed
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
PSQI	Pittsburgh Sleep Quality Index
PT	prothrombin time
q4w	Every 4 weeks
QMS	Quality Management System
QoL	Quality of Life
RBC	Red blood cell(s)
rem	roentgen equivalent man
s.c.	subcutaneous
SAE	serious adverse event
SCR	Screening
SD	standard deviation
SF-36	Medical Outcome Short Form (36) Health Survey
SF-36 PCS	Short Form-36 Physical Component Summary
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SI	Sacroiliac
SIJ	Sacroiliac Joint
SOP	Standard operating procedure
SpA	Spondyloarthritis
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
Sv	sievert (1 milliSv (mSv) = 100 millirem (mrem))
t.i.d	three times a day
TBIL/TBL	total bilirubin
TNF-IR	TNFα Inhibitor Incomplete Responder
TNF/TNFα	Tumor Necrosis Factor
ts-DMARD	targeted synthetic Disease Modifying Anti-rheumatic Drug
ULN	upper limit of normal
US	United States

VAS	Visual Analog Scale
vs.	versus
WBC	white blood cell(s)
WHO	World Health Organization
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.

Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject 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	CAIN457P12301
Full Title	A randomized, double-blind, placebo-controlled, parallel group, phase III multicenter study of intravenous secukinumab to compare efficacy at 16 weeks with placebo and to assess safety and tolerability up to 52 weeks in subjects with active Ankylosing Spondylitis or non-radiographic axial SpondyloArthritis
Brief title	Study to demonstrate the efficacy, safety and tolerability of an intravenous (i.v.) regimen of secukinumab compared to placebo in subjects with active axSpA
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this global study is to demonstrate the efficacy, safety, and tolerability of an intravenous (i.v.) regimen of secukinumab compared to placebo in subjects with active axSpA at Week 16 despite current or previous NSAID, DMARD and/or anti Tumor Necrosis Factor (TNF) therapy. In addition, to further support efficacy and safety of an i.v. regimen, data will be collected for up to 52 weeks of treatment. Efficacy and safety data may be used to support the registration of i.v. secukinumab in the US and other countries for treatment of subjects with active axSpA.
Primary Objective(s)	To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo in subjects with active axspA (AS and nr-axSpA) based on the proportion of subjects achieving an ASAS40 (Assessment of SpondyloArthritis International Society criteria) response.
Secondary Objectives	1. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) major improvement 2. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) 3. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects meeting the ASAS 5/6 response criteria 4. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on Bath Ankylosing Spondylitis Functional Index (BASFI) 5. To evaluate the efficacy of i.v. secukinumab compared to placebo after 16 weeks of treatment by assessing Short Form-36 Physical Component Summary (SF-36 PCS) 6. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores 7. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in high sensitivity C-Reactive Protein (hsCRP)

	8. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response 9. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) inactive disease 10. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving ASAS partial remission 11. To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in Pittsburgh Sleep Quality Index (PSQI) 12. Overall safety and tolerability of i.v. secukinumab compared to placebo as assessed by physical exams, vital signs, laboratory assessments and adverse event monitoring
Study design	This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design to study the efficacy, safety, and tolerability of treatment with intravenous secukinumab (initial dose of 6 mg/kg followed thereafter with 3 mg/kg administered every four weeks starting at Week 4) in subjects with active axSpA.
Population	The study population will consist of male and female subjects (≥18 years old at the time of consent) with active axSpA (radiographic AS or non-radiographic axSpA). The diagnosis of axSpA must fulfill the ASAS criteria of inflammatory back pain for at least 6 months AND onset before 45 years of age. The diagnosis of radiographic AS must fulfill the Modified New York criteria for ankylosing spondylitis with prior documented radiological evidence (x-ray or a radiologists report). Subjects with nr-axSpA (no definitive radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS) must fulfill the following ASAS classification criteria for axSpA: a. Sacroiliitis on MRI with ≥ 1 SpA feature OR HLA-B-27 is positive with ≥2 SpA features AND b. Objective signs of inflammation at screening, evident by either MRI with SI joint inflammation AND / OR hsCRP > ULN (as defined by the central lab) In addition, all subjects must have evidence of active axSpA as measured by the following three assessments: • total BASDAI ≥4 cm on a scale of 0-10 cm • spinal pain as measured by BASDAI question #2 ≥4 cm (0-10 cm) • total back pain as measured by visual analog scale (VAS) ≥40 mm (0-100 mm) Included subjects must have evidence of active disease despite current or previous NSAID, conventional DMARD and/or anti-TNF therapy. This is a global interventional study and it expected that approximately 500 subjects are randomized (400 with active AS and 100 with nr-axSpA) to evaluate the efficacy and safety of intravenous secukinumab in this subject population.
Key Inclusion criteria	1. Subject must be able to understand and communicate with the investigator, comply with the requirements of the study. and must give written, signed and dated informed consent before any study assessment is performed 2. Male and non-pregnant, non-lactating female patients ≥ 18 years of age 3. Diagnosis of axSpA according to ASAS criteria

	a. Inflammatory back pain for at least 6 months b. Onset before 45 years of age 4. For subjects with AS: Diagnosis of moderate to severe AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS 5. For subjects with nr-axSpA: X-ray of SIJ negative (centrally read) for AS by Modified NY criteria AND a. Sacroiliitis on MRI (centrally read) with ≥ 1 SpA feature OR HLA-B-27 positive with ≥2 SpA features AND b. Objective signs of inflammation at screening, evident by either MRI with SIJ inflammation (centrally read) AND / OR hsCRP > ULN (as defined by the central lab) 6. Active axial SpA assessed by BASDAI ≥4 cm (0-10 cm) at Baseline 7. Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) at Baseline 8. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) at Baseline 9. Subjects should have had inadequate response or failure to respond to at least 2 NSAIDs at an approved dose for a minimum of 4 weeks in total and a minimum of 2 weeks for each NSAID prior to randomization, or less than 4 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications 10. Subjects who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS or nr-axSpA therapy are required to be on a stable dose for at least 2 weeks before randomization 11. Subjects who are intolerant or have been inadequate responders to a TNF inhibitor (not more than one) will be allowed to enter into the study (not more than 20% per group). They must have experienced an inadequate response to previous or current treatment at an approved dose for at least 3 months prior to randomization, or have been intolerant to at least one administration of an anti-TNF agent. These subjects will undergo an appropriate wash-out period prior to randomization, if required a. 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours b. 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days c. 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) d. 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days e. 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days 12.Subjects taking methotrexate (MTX) (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization. Subjects on MTX must be on folic acid supplementation before randomization 13. Subjects who are on a conventional DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which must be be discontinued 8 weeks prior to randomization, unless a cholestyramine washout has been performed

	14.Subjects taking systemic corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization
Key Exclusion criteria	Subjects meeting any of the following criteria are not eligible for inclusion in this study 1. Subjects with total ankylosis of the spine 2. 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 3. Subjects taking moderate and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine) 4. Presence of significant medical problems which at investigator's discretion, will prevent the subject from participating in the study, including but not limited to the following: Subjects with severely reduced kidney function (estimated glomerular filtration rate (eGFR) <29 ml/min/1.73m^2), 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) 5. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization 6. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy 7. 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 8. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis 9. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule in Table 8-1. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated 10. Past medical history of infection with HIV or hepatitis B prior to randomization or active infection or on treatment for Hepatitis C at randomization 11. History of lymphoproliferative disease or any known malignancy, or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed) 12. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)

	13. 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 hCG laboratory test 14. Screening total WBC count <3,000/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl (85 g/L) 15. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST), SGPT (ALT), alkaline phosphatase and serum bilirubin. The investigator should be guided by the following criteria: · Any single parameter may not exceed 2 x the upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to randomization, to rule-out laboratory error. · If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L) 16. 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 precluding ability to perform self-care 17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU) 18. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis 19. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial 20. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations 21. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor 22. 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)
Study treatment	At baseline, subjects with active AS and nr-axSpA will be randomized to one of the two treatment groups: Group 1: approximately 200 AS subjects and 50 nr-axSpA subjects; These subjects will receive secukinumab 6 mg/kg i.v. at randomization (Baseline (BSL) visit), followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 4 through Week 48 (exposure through week 52). Group 2: approximately 200 AS subjects and 50 nr-axSpA subjects; These subjects will receive i.v. placebo at randomization (BSL visit), Weeks 4, 8, and 12 , followed

	by the administration of secukinumab 3 mg/kg i.v. at Week 16 and every four weeks through Week 48 (exposure through week 52).
Efficacy assessments	• Assessment of SpondyloArthritis International Society (ASAS) response criteria; ASAS40, ASAS20, ASAS 5/6 and ASAS partial remission • Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) • Bath Ankylosing Spondylitis Disease Activity Index 50 (BASDAI50) • Bath Ankylosing Spondylitis Functional Index (BASFI) • Patient's global assessment of disease activity (VAS) • Patient's assessment of back pain intensity (VAS) [redacted] • Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form) • Ankylosing Spondylitis Quality of Life (ASQoL) • High sensitivity C-Reactive Protein (hsCRP) [redacted] • Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) and ASDAS response categories [redacted] • Sleep improvement ([redacted] sleep PROs)
Key safety assessments	• Physical examination • Vital signs • Height and weight • QuantiFERON TB-Gold test or PPD skin test • Hepatitis and human immunodeficiency virus (HIV) screen • Laboratory evaluations (Hematology, clinical chemistry, lipid panel, cardiovascular Panel, urinalysis and pregnancy test) • Evaluation of AE/ SAE's • Local tolerability (Injection site reactions) • Pregnancy and assessment of fertility • Tolerability of secukinumab [redacted]
Other assessments	• Quality of Life questionnaires/ Patient reported outcomes (PROs) • Trial Feedback Questionnaires [redacted] • HLA-B27 • Pharmacokinetics [redacted] • Activity/Mobility improvement • Sacroiliac Joint X-ray • Sacroiliac Joint MRI
Data analysis	The primary endpoint in the study is the proportion of subjects who achieve an ASAS40 response at Week 16. The statistical hypothesis for ASAS40 being tested

	is that there is no difference in the proportion of subjects fulfilling the ASAS40 criteria at Week 16 in the secukinumab i.v. regimen versus placebo. Let p_0 denote the proportion of ASAS40 responders at Week 16 for placebo regimen and p_1 denote the proportion of ASAS40 responders at Week 16 for secukinumab i.v. regimen. In statistical terms, H_1: $p_1 = p_0$, H_{A1}: $p_1 \neq p_0$, i.e., H_1: secukinumab i.v. regimen is not different to placebo regimen with respect to ASAS40 response at Week 16 The primary endpoint of ASAS40 at Week 16 in the FAS will be evaluated using a logistic regression with treatment and randomization stratum (disease condition) as factors and weight as a covariate. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model for the comparison of secukinumab i.v. regimen versus placebo. The secondary endpoints include ASDAS-CRP major improvement, BASDAI, ASAS 5/6, BASFI, SF-36 PCS, ASQoL, hsCRP, ASAS20, ASDAS-CRP inactive disease, ASAS partial remission and PSQI at Week 16. The binary secondary endpoints (e.g., ASAS 5/6, etc.) will be evaluated via a logistic regression with treatment and randomization stratum (disease condition) as factors and weight as a covariate. The change from baseline in continuous secondary endpoints (e.g., BASDAI, etc.) will be evaluated using MMRM with treatment group, stratification factor (disease condition) and analysis visit as categorical factors, baseline measure and weight as continuous covariates, and treatment by analysis visit and baseline measure by analysis visit as interaction terms. An unstructured covariance structure will be assumed for the model. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs.
Key words	Active axSpA, Axial spondyloarthritis, non-radiographic-axSpA, nr-axSpA, ankylosing spondylitis, AS, inflammatory back pain, sacroiliitis, intravenous secukinumab

1 Introduction

1.1 Background

Axial spondyloarthritis (axSpA) is a type of spondyloarthritis mainly affecting the axial skeleton, characterized by spinal inflammation and inflammatory back pain. AxSpA is among the most common chronic inflammatory joint disorders, with recent estimates of prevalence in Caucasian populations in the range of 1–2% (Baraliakos and Braun 2011). Patients with chronic back pain (onset before 45 years of age) are classified as having axSpA if they fulfill either the clinical arm or the imaging arm of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria (Rudwaleit et al 2009).

Based on the presence or absence of sacroiliitis on conventional X-ray radiographs, axSpA patients are further classified into two conditions: non-radiographic-axSpA (nr-axSpA) and ankylosing spondylitis (AS). Patients with evidence of sacroiliitis on X-ray fulfilling the 1984 modified New York diagnostic criteria (van der Linden et al 1984) are classified as having AS, whereas patients who do not show sacroiliitis on X-ray, but may show evidence of sacroiliitis on MRI, are classified as having nr-axSpA.

AS is characterized mainly by involvement of the axial skeleton and sacroiliac (SI) joints, but peripheral joints, entheses and extra-articular organs may also be affected. A significant proportion of AS patients may present with associated extra-articular manifestations such as uveitis, psoriasis, inflammatory bowel disease (IBD), or cardiovascular and pulmonary abnormalities. Generalized osteoporosis, as well as regional osteopenia are common in AS patients and predispose them to non-traumatic fractures, despite a predominantly younger age and male gender distribution. The presence of the Human Leukocyte Antigen (HLA)-B27 is strongly associated with AS; 90–95% of patients with AS who have European ancestry carry this marker. AS affects up to 1.1% of the population, is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden.

Studies and registry data have shown that nr-axSpA patients have similar levels of disease activity, pain, and health-related quality of life impairment as observed in AS patients (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 is a disease with distinct stages (Song et al 2013). Furthermore, with a longer duration of symptoms, most patients who start with nr-axSpA ultimately develop radiographic evidence consistent with AS. In an investigation of 329 patients with axSpA, evidence of radiographic sacroiliitis was present in 40-86% of patients, in accordance with the duration of symptoms (<10 to > 20 years) (Said-Nahal et al 2000), with many nr-axSpA patients progressing to AS over time. Nonetheless, it is estimated that 10-15% of nr-axSpA patients do not develop radiographic sacroiliitis (Sieper and van der Heijde 2013). Thus, nr-axSpA may represent an early stage of AS, but may also be a form of the disease which causes much pain without leading to structural changes of the axial skeleton (Baraliakos and Braun 2015). In short, patients recognized as having axSpA, either with AS or nr-axSpA, present with similar clinical characteristics, the same burden of disease, and the same response to anti-inflammatory medication. A study evaluating the efficacy and safety of secukinumab 150 mg s.c. q4w vs. placebo (CAIN475H2315) in patients with nr-axSpA is currently ongoing.

First-line medication of mild AS consists of non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAID-refractory AS is hampered by the lack of efficacy of virtually all conventional disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX). As an exception, peripheral arthritis associated with AS may respond to sulfasalazine and methotrexate. TNF blocking agents were successfully added to the armamentarium to treat AS (Braun et al 2002) and subsequently demonstrated prolonged efficacy up to eight years of follow-up (Baraliakos et al 2011). However, upon discontinuation of TNF blockers the disease relapses quickly (Baraliakos et al 2005), indicating that the inflammatory process may have only been inhibited but not completely abolished.

Secukinumab is a fully human IgG1 antibody that selectively binds to and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab targets IL-17A, inhibiting its interaction with the IL-17 receptor expressed on various cell types including keratinocytes and synoviocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases, including psoriasis, psoriatic arthritis (PsA) and AS.

To date, s.c. secukinumab is approved in over 90 countries for the clinical management of PsA and AS.

1.2 Purpose

The purpose of this global study is to demonstrate the efficacy, safety, and tolerability of an intravenous (i.v.) regimen of secukinumab compared to placebo in subjects with active axSpA, including AS and nr-axSpA at Week 16 despite current or previous NSAID, conventional DMARD and/or anti TNF therapy. In addition, to further support efficacy and safety of an i.v. regimen, data will be collected for up to 52 weeks of treatment. Efficacy and safety data may be used to support the registration of i.v. secukinumab in the US and other countries for treatment of subjects with active axSpA.

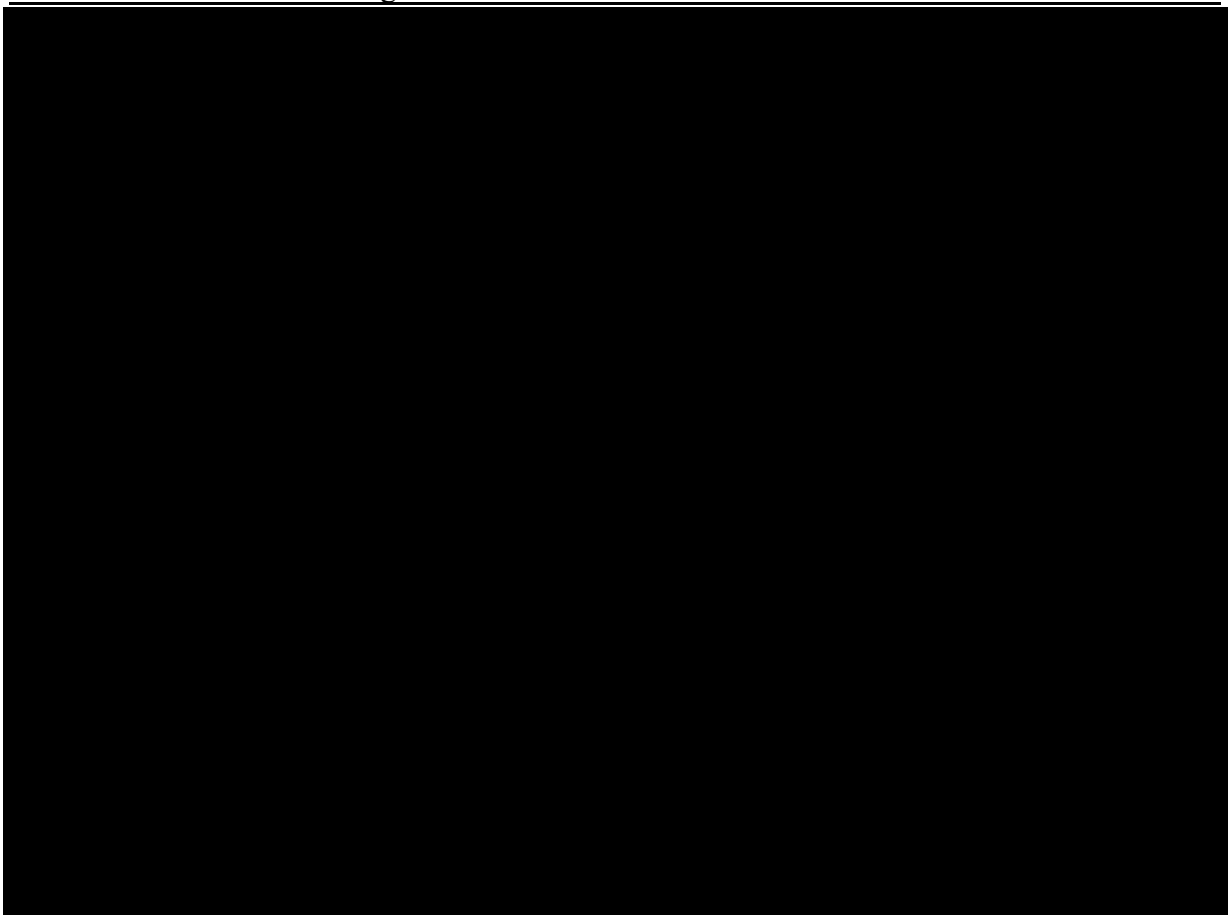
2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

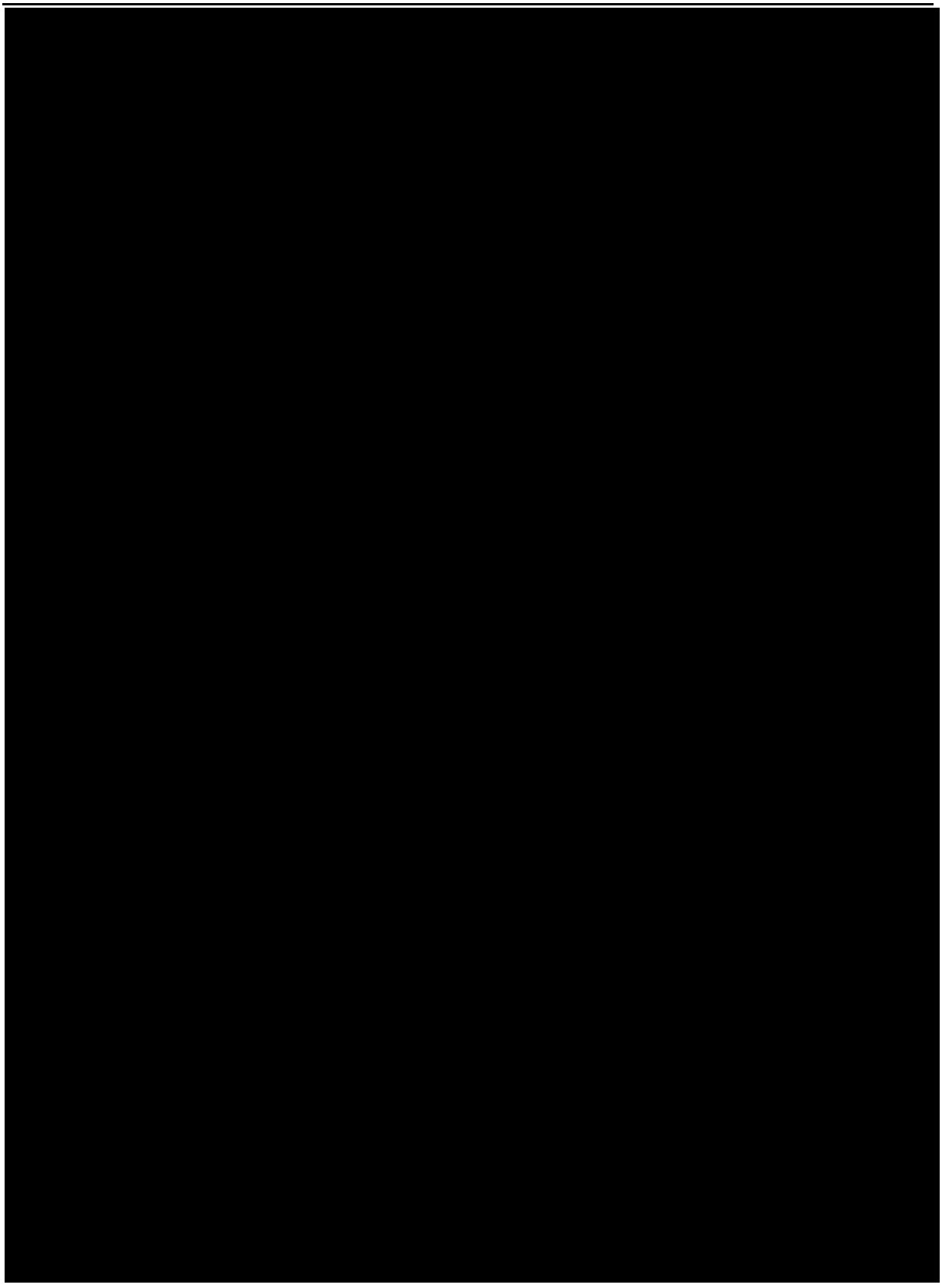
Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo in subjects with active axSpA (AS and nr-axSpA) based on the proportion of subjects achieving an ASAS40 (Assessment of SpondyloArthritis International Society criteria) response.	• ASAS40 response at Week 16, defined as improvement of ≥ 40% and an absolute improvement from baseline of ≥20 units (range 0–100) in ≥ 3 of the following 4 domains: back pain [10 cm visual analogue scale (VAS)], patient global assessment of disease activity (10 cm VAS), physical function (BASFI; range 0–100) and inflammation (mean score

Objective(s)	Endpoint(s)
	of items 5 and 6 of the BASDAI; both 10 cm VAS) without any worsening in the remaining domain.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) major improvement	• ASDAS-CRP major improvement defined as a change (decrease) in the score of at least 2.0 units
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in total Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	• Change from baseline in total BASDAI
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects meeting the ASAS 5/6 response criteria	• Subjects achieving ASAS 5/6 response defined as: improvement of ≥20% in at least five of six domains
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on Bath Ankylosing Spondylitis Functional Index (BASFI)	• Change from baseline of BASFI
• To evaluate the efficacy of i.v. secukinumab compared to placebo after 16 weeks of treatment by assessing Short Form-36 Physical Component Summary (SF-36 PCS)	• Absolute & percent change from baseline in SF-36 PCS
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) scores	• Absolute & percent change from baseline in ASQoL
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in high sensitivity C-Reactive Protein (hsCRP)	• Change from baseline in hsCRP
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving an ASAS20 response	• The ASAS Response Criteria (ASAS20) is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and

Objective(s)	Endpoint(s)
	≥1 unit on a scale of 10 in the remaining domain.
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) inactive disease	• ASDAS-CRP inactive disease as defined by an ASDAS-CRP score below 1.3
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the proportion of subjects achieving ASAS partial remission	• ASAS partial remission criteria are defined as a value not above 2 units in each of the four main ASAS domains on a scale of 0-10
• To demonstrate that the efficacy of i.v. secukinumab at Week 16 is superior to placebo based on the change from baseline in Pittsburgh Sleep Quality Index (PSQI)	• Change from baseline in PSQI
• Overall safety and tolerability of i.v. secukinumab compared to placebo as assessed by physical exams, vital signs, laboratory assessments and adverse event monitoring	• Physical exams, vital signs, laboratory assessments, and adverse event monitoring



Objective(s)	Endpoint(s)
[redacted]	



Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design to study the efficacy, safety, and tolerability of treatment with intravenous secukinumab (initial dose of 6 mg/kg followed thereafter with 3 mg/kg administered every four weeks starting at Week 4) in subjects with active axSpA. The study population consists of approximately 400 subjects with active AS and approximately 100 subjects with active nr-axSpA, despite current or previous NSAID, conventional DMARD and / or TNF inhibitor therapy, or intolerance to these therapies. A screening (SCR) period of up to 10 weeks will be used to assess eligibility, followed by randomization to 52 weeks of study treatment.

At baseline, subjects with active AS and nr-axSpA will be randomized to one of the two treatment groups:

- Group 1: approximately 200 AS subjects and approximately 50 nr-axSpA subjects; These subjects will receive secukinumab 6 mg/kg i.v. at randomization (Baseline (BSL) visit), followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 4 through Week 48 (exposure through Week 52).
- Group 2: approximately 200 AS subjects and approximately 50 nr-axSpA subjects; These subjects will receive i.v. placebo at randomization (BSL visit), Weeks 4, 8, and 12 ,

followed by the administration of secukinumab 3 mg/kg i.v. at Week 16 and every four weeks through Week 48 (exposure through Week 52).

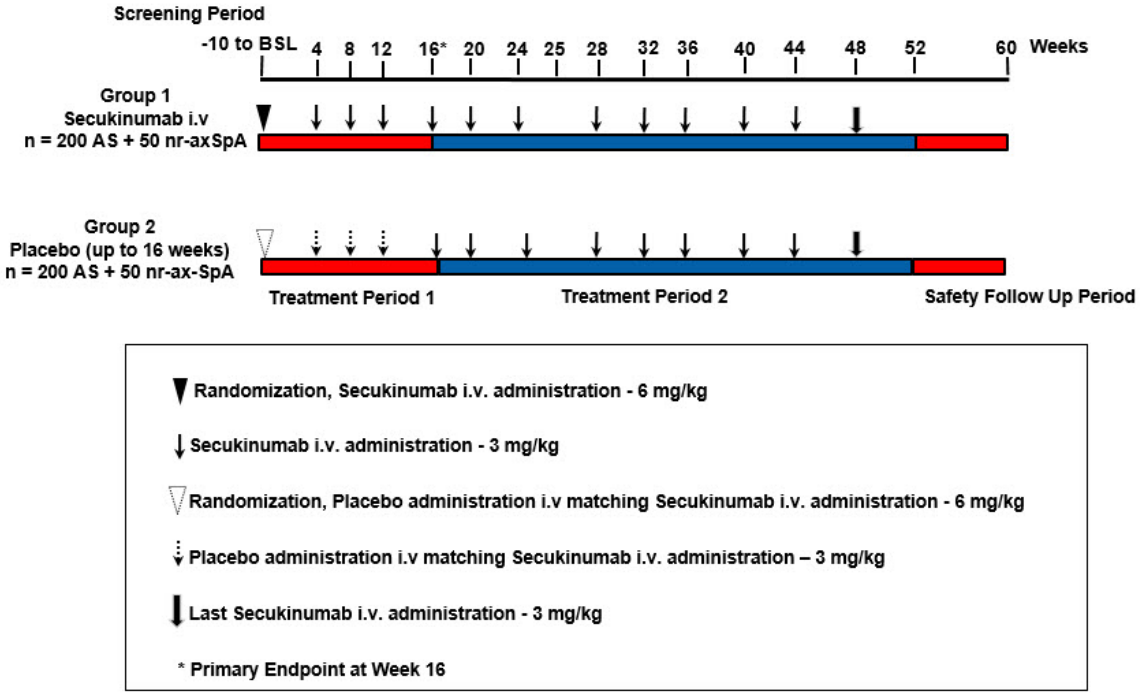
This study will consist of 4 periods totaling 70 weeks: the screening period (up to 10 weeks), the treatment period 1 (total duration of 16 weeks) and the treatment period 2 (total duration of 36 weeks) followed by the safety follow up period of 8 weeks after the end of treatment visit (i.e., Week 52).

The subjects will be stratified at randomization according to disease condition (i.e., AS or nr-axSpA). No more than 20% TNF Inhibitor Incomplete Responders (TNF-IR) subjects will be enrolled in the study. Starting at Week 16, all subjects will switch to open-label intravenous secukinumab, including all placebo subjects.

No subject will be on placebo treatment after Week 16, because axSpA is considered a chronic disease with no 'true' and lasting placebo response. However, all subjects and investigators/site staff will remain blinded to the original randomized treatment group assignment (secukinumab treatment vs placebo). Study treatment will continue up to Week 52. An end of treatment visit (i.e., Week 52) is to be done 4 weeks after last study treatment administration and a post treatment follow-up visit (i.e., Week 60) is to be done 8 weeks after the end of treatment visit for all subjects (regardless of whether they complete the entire study as planned or discontinue prematurely). All i.v. infusions will be performed at the study site and site personnel will administer the infusions to subjects.

Rescue medication is not allowed until Week 16. However, subjects who are deemed by the investigator 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. The study will have a primary endpoint analysis at Week 16. Therefore, the primary analysis will be performed with Week-16 data once the last subject has completed the Treatment Period 1.

Figure 3-1 Study Design



4 Rationale

4.1 Rationale for study design

The double-blind, randomized, parallel-group, placebo-controlled design used in this study is aligned with Phase III trials of other biologics and is in accordance with EMA (European Medical Agency) guidelines (EMA 2017) and available precedent. The treatment duration of the placebo group has been kept short and the group will be re-assigned to active treatment once the Week 16 visit for primary endpoint assessments has been reached. Although study treatment is open label secukinumab i.v. starting at Week 16, blinding to original treatment assignment will be maintained, so as to ensure unbiased efficacy and safety assessments for the remainder of the study.

A non-dosing visit has been included at Week 25. Efficacy measures and a PK sample collected at that visit will be used to assess the dynamic of the efficacy response in steady or quasi-steady state condition between the administration of two doses as well as its relationship with secukinumab concentration. This will allow exploration of the possible effect of the route of administration on the efficacy response.

4.1.1 Rationale for choice of background therapy

Clinical management of axSpA by pharmacotherapy includes the use of NSAIDs and conventional DMARDs, and if insufficient response, biologic agents (i.e., TNF-inhibitor therapy or anti-IL17 agents).

This study intends to enroll patients with active disease despite current or previous NSAIDs, conventional DMARDs and/or TNF inhibitor therapy or intolerance to these therapies. A background of NSAID therapy and/or concomitant therapy with methotrexate (≤25 mg/week) or sulfasalazine (≤ 3 g/day) will be acceptable, if dose and route of administration have been stable for at least two weeks with NSAIDs and/or four weeks with MTX or sulfasalazine, prior to the randomization visit. Inclusion of patients with active axSpA who are TNF-IR (up to 20% in each group) in the study also makes the background patient population more representative of the real world clinical scenario.

4.2 Rationale for dose/regimen and duration of treatment

[redacted]

[redacted] Hence, the proposed i.v. regimen is expected to deliver an exposure within the approved s.c. doses of secukinumab. Considering the large amount of clinical data collected so far and understanding of the PK profile for secukinumab in AS, it is expected that the clinical response with the proposed i.v. regimen will be similar to that observed with current approved s.c. regimens.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

A placebo arm up to the primary endpoint at Week 16 is included in this study. Due to the nature of the disease and the outcome measures used (ASAS criteria), a placebo arm is necessary to reliably evaluate the efficacy and safety of the active drug. The continuation of the placebo

group up to the primary endpoint assessment at Week 16 can be supported from an ethical standpoint, as subjects can continue on a range of concomitant treatments.

The parallel-group placebo controlled design used in this study is aligned with Phase III trials of other biologics in this disease area including registration studies of s.c. secukinumab in axSpA and is also in accordance with EMA guidelines (EMA 2017). The treatment duration of the placebo group is relatively short and the placebo group will be re-assigned to active treatment at Week 16. The regular assessment of disease activity ensures that subjects who are experiencing worsening of disease in any of the treatment groups can exit the study at any time upon their own accord or based on the advice of the investigator.

4.4 Purpose and timing of interim analyses/design adaptations

The primary endpoint analysis (Week-16 analysis) will be performed after all subjects complete the Week-16 visit in order to support regulatory filings.

Additional analyses may be performed to support health authority interactions, as necessary.

The investigators, site personnel, subjects and monitors will remain blinded to the original treatment assignment groups until Week-60 analysis has been completed.

4.5 Risks and benefits

Secukinumab has demonstrated either preliminary or confirmed efficacy in several inflammatory diseases including psoriasis, psoriatic arthritis and ankylosing spondylitis. The safety profile of secukinumab is primarily based on the aggregate safety data from 10 large completed phase II/III psoriasis trials. The evaluation of safety data from completed phase II/III AS trials did not show additional safety concerns.

Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events are infections, especially upper respiratory tract with secukinumab relative to placebo.

There was an increase in mucosal or cutaneous candidiasis with secukinumab compared to placebo, but the cases were mostly mild or moderate in severity, non-serious, and responsive to standard treatment.

There was a small increase in mild neutropenia cases with secukinumab compared to placebo.

Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5×10^9/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections.

Hypersensitivity reactions including urticarial and a rare event of anaphylactic reaction to secukinumab were also observed in clinical studies.

Taking into account the individual risks as outlined above, the expected risk profile of the i.v. regimen of secukinumab from a mechanism of action perspective is anticipated to be similar to that seen with the approved s.c. secukinumab regimens. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and extensive guidance to the investigators, provided in the current version of the Investigator's Brochure (IB).

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

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

5 Population

The study population will consist of male and female subjects (≥18 years old at the time of consent) with active axSpA (AS or nr-axSpA). The diagnosis of axSpA must fulfill the ASAS criteria of inflammatory back pain for at least 6 months AND onset before 45 years of age. For a diagnosis of AS, subjects must fulfill the Modified New York criteria for AS (see Section 16.2) with prior documented radiological evidence (x-ray or a radiologists report).

Subjects with nr-axSpA (no definitive radiographic evidence of changes in the sacroiliac joints that would meet the modified New York criteria for AS) must fulfill the following ASAS classification criteria for axSpA:

a. Sacroiliitis on MRI (centrally read) with ≥ 1 SpA feature OR HLA-B27 is positive with ≥2 SpA features AND
b. Objective signs of inflammation at screening, evident by either MRI with SI joint inflammation (centrally read) AND / OR hsCRP > ULN (as defined by the central lab)

In addition, all subjects must have evidence of active axSpA as measured by the following three assessments:

- total BASDAI ≥4 cm on a scale of 0-10 cm
- spinal pain as measured by BASDAI question #2 ≥4 cm (0-10 cm)
- total back pain as measured by visual analog scale (VAS) ≥40 mm (0-100 mm)

Included subjects must have evidence of active disease despite current or previous NSAID, conventional DMARD and/or anti-TNF therapy.

This is a global interventional study and it is expected that approximately 500 subjects are randomized (approximately 400 subjects with active AS and approximately 100 subjects with nr-axSpA) to evaluate the efficacy and safety of i.v. secukinumab in this subject population.

A screening failure rate of 25% and post-randomization drop-out rate of 10% prior to the time of the primary endpoint assessments (Week 16) are anticipated. Enrollment will stop as soon as the target number of randomized subjects is reached.

No more than 20% TNF-IR subjects will be enrolled in the study.

Subjects can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the subject. Mis-randomization occurs when a subject who does not meet all eligibility criteria receives a randomization number in IRT in error; mis-randomized subjects will be treated as screen failures and will not be re-screened. However, if the subject randomized in error was dosed then he/she will be discontinued.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Subject must be able to understand and communicate with the investigator, comply with the requirements of the study. and must give written, signed and dated informed consent before any study assessment is performed
2. Male and non-pregnant, non-lactating female patients ≥ 18 years of age
3. Diagnosis of axSpA according to ASAS criteria
   a. Inflammatory back pain for at least 6 months
   b. Onset before 45 years of age
4. For subjects with AS: Diagnosis of AS with prior documented radiologic evidence (x-ray or radiologist's report) fulfilling the Modified New York criteria for AS
5. For subjects with nr-axSpA:
   X-ray of SIJ negative (centrally read) for AS by Modified NY criteria AND
   a. Sacroiliitis on MRI (centrally read) with ≥ 1 SpA feature OR HLA-B-27 positive with ≥2 SpA features AND
   b. Objective signs of inflammation at screening, evident by either MRI with SIJ inflammation (centrally read) AND / OR hsCRP > ULN (as defined by the central lab)
6. Active axial SpA assessed by BASDAI ≥4 cm (0-10 cm) at Baseline
7. Spinal pain as measured by BASDAI question #2 ≥ 4 cm (0-10 cm) at Baseline
8. Total back pain as measured by VAS ≥ 40 mm (0-100 mm) at Baseline
9. Subjects should have had inadequate response or failure to respond to at least 2 NSAIDs at an approved dose for a minimum of 4 weeks in total and a minimum of 2 weeks for each NSAID prior to randomization, or less than 4 weeks if therapy had to be withdrawn due to intolerance, toxicity or contraindications
10. Subjects who are regularly taking NSAIDs (including COX-1 or COX-2 inhibitors) as part of their AS or nr-axSpA therapy are required to be on a stable dose for at least 2 weeks before randomization
11. Subjects who are intolerant or have been inadequate responders to a TNF inhibitor (not more than one) will be allowed to enter into the study (not more than 20% per group). They must have experienced an inadequate response to previous or current treatment at an approved dose for at least 3 months prior to randomization, or have been intolerant to at least one administration of an anti-TNF agent. These subjects will undergo an appropriate wash-out period prior to randomization, if required
    a. 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours
    b. 8 weeks for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days
    c. 10 weeks for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks)
    d. 10 weeks for Simponi® (golimumab) – with a terminal half-life of 11-14 days
    e. 10 weeks for Cimzia® (certolizumab) – with a terminal half-life of 14 days

12. Subjects taking methotrexate (MTX) (≤ 25 mg/week) or sulfasalazine (≤ 3 g/day) are allowed to continue their medication and must have taken it for at least 3 months and have to be on a stable dose for at least 4 weeks prior to randomization. Subjects on MTX must be on folic acid supplementation before randomization
13. Subjects who are on a conventional DMARD other than MTX or sulfasalazine must discontinue the DMARD 4 weeks prior to randomization, except for leflunomide, which must be be discontinued 8 weeks prior to randomization, unless a cholestyramine washout has been performed
14. Subjects taking systemic corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study

1. Subjects with total ankylosis of the spine
2. 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
3. Subjects taking moderate and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
4. Presence of significant medical problems which at investigator's discretion, will prevent the subject from participating in the study, including but not limited to the following: Subjects with severely reduced kidney function (estimated glomerular filtration rate (eGFR) <29 ml/min/1.73m^2), 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)
5. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before Randomization
6. Underlying conditions (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy
7. 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
8. Active systemic infections during the last two weeks (exception: common cold) prior to randomization or any infection that reoccurs on a regular basis
9. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5 mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule in Table 8-1. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
10. Past medical history of infection with HIV or hepatitis B prior to randomization or active infection or on treatment for Hepatitis C at randomization

11. History of lymphoproliferative disease or any known malignancy, or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
12. Use or planned use of prohibited concomitant medication (see Section 6.2.2)
13. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
14. 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 hCG laboratory test
15. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
16. Screening total WBC count <3,000/µl, or platelets <100,000/µl or neutrophils <1,500/µl or hemoglobin <8.5 g/dl (85 g/L)
17. History of clinically significant liver disease or liver injury indicated by abnormal liver function tests, such as SGOT (AST), SGPT (ALT), alkaline phosphatase and serum bilirubin. The investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x the upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to randomization, to rule-out laboratory error.
    - If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L)
18. 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 precluding ability to perform self-care
19. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomization
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. 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 six 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: 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 and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. 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.

21. Active ongoing inflammatory diseases other than axSpA that might confound the evaluation of the benefits of secukinumab therapy, including inflammatory bowel disease or uveitis
22. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial
23. Use of other investigational drugs at the time of enrollment, or within 5 half- lives of enrollment, or within 4 weeks until the expected pharmacodynamic effect has returned to baseline, whichever is longer; or longer if required by local regulations
24. History of hypersensitivity to any of the study drug constituents
25. Previous exposure to secukinumab (AIN457) or any other biologic drug directly targeting IL-17 or the IL-17 receptor
26. 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)

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply the following study treatments:

Investigational Treatment:

- Secukinumab liquid in vial (LiV) for i.v. infusion provided in glass vials, [redacted]

Reference Therapy:

- Secukinumab placebo [redacted] for i.v. infusion provided in 5 mL LiV.

The LiV glass vials are packed in double-blind (treatment period 1, up to and including Week 12) and open label fashion (treatment period 2, from Week 16 onwards). For detailed instructions for storage, handling and administration of study treatment, please refer to the Pharmacist Manual.

The study medication will be labeled as follows:

- Double blind Secukinumab Liquid in Vial will be labeled as AIN457 [redacted] Placebo.
- Open label Secukinumab Liquid in Vial will be labeled as AIN457 [redacted]

6.1.2 Additional study treatments

No other treatment/s beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

At baseline, all eligible subjects will be randomized to one of the two treatment arms in a 1:1 ratio via Interactive Response Technology (IRT):

- Group 1: 200 AS subjects and 50 nr-axSpA subjects ; These subjects will receive secukinumab 6 mg/kg i.v. at randomization (i.e. BSL), followed by the administration of secukinumab 3 mg/kg i.v. every four weeks starting at Week 4 through Week 48 (exposure through Week 52).
- Group 2: 200 AS subjects and 50 nr-axSpA subjects ; These subjects will receive i.v. placebo at randomization (i.e. BSL) and at Weeks 4, 8, and 12, followed by the administration of secukinumab 3 mg/kg i.v. at Week 16 and every four weeks through Week 48 (exposure through Week 52).

All subjects will receive blinded treatment every four weeks starting at baseline and until Week 16. At Week 16, subjects from Group 1 will continue using secukinumab 3 mg/kg i.v. and subjects from Group 2 will start receiving secukinumab 3 mg/kg i.v. every four weeks (see Figure 3-1).

Treatment will be provided open-label from Week 16 onwards, as all subjects will be receiving 3 mg/kg i.v. every 4 weeks; however, the investigators, site personnel, subjects and monitors will remain blinded to initial randomized group assignment.

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier (see Section 9.1.1) due to unacceptable toxicity, disease progression and/or at the discretion of the investigator or the subject.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is provided in this trial.

6.2.1 Concomitant therapy

The investigator should instruct the subject to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) administered after the subject was enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the Prior and Concomitant medications or Procedures and Significant Non Drug Therapy eCRF. The reason, name of the drug, procedure or non-drug therapy should be listed.

Guidelines for the use of specific medications are provided below:

Methotrexate (MTX)

Subjects taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 16.

Folic acid

Subjects on MTX must be taking folic acid supplementation before randomization and during the trial to minimize the likelihood of MTX associated toxicity.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The subject should remain on a stable dose until Week 16.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 16, although the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding eCRF page.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 16. After Week 16, no more than 1 joint per 24-week period may be injected . No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any 52-week period. Injection of intra-articular steroids is not permitted within 8 weeks prior to Week 52.

Non-steroidal anti-inflammatory drugs (NSAIDs) (including COX-1 or COX-2 inhibitors), low strength opioids and acetaminophen/paracetamol

Subjects on regular use of NSAIDs or paracetamol/acetaminophen should be on stable dose for at least 2 weeks before randomization to allow inclusion in the study.

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN within the 2 weeks before randomization can continue to do so in the study; however, they have to refrain from any intake during at least the 24 hours before a visit with disease activity assessment. Regular dosing with low strength opioids is not permitted.

After the Week 16 assessments are completed, a change in the NSAID intake regimen is permitted.

Any change of the NSAID/paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-1 is NOT allowed after the start of the washout period unless specified otherwise below. Live vaccines should not be given until 12 weeks after last study treatment administration.

Table 6-1 Prohibited medication

Medication	Washout period (before randomization)	Action (after randomization)
Any biologic drugs, including but not limited to TNFα inhibitors, secukinumab, or other biologic drugs targeting IL-17 or IL-17 receptor	Biological immunomodulating agents > 3 different TNFα Inhibitors: never	Discontinue investigational treatment
Etanercept	4 weeks	
Infliximab	8 weeks	
Adalimumab, golimumab, certolizumab	10 weeks	
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g., alemtuzumab (Campath), anti-CD4, anti-CD5, anti-CD3, and anti-CD19]	Never	Discontinue investigational treatment
Conventional synthetic DMARDs (with the exception of MTX and sulfasalazine) and ts-DMARDs including apremilast, tofacitinib, etc.	4 weeks	Discontinue investigational treatment
Leflunomide	8 weeks	Discontinue investigational treatment
Leflunomide with cholestyramine washout[#]	4 weeks	Discontinue investigational treatment
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)	Discontinue investigational treatment
Unstable dose of NSAIDs (including selective COX-1 and COX-2 inhibitors)	2 weeks	Dose adjustments allowed after Week 16 Discontinuation of investigational treatment may be required on a case by case basis.
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN[+]	2 weeks	Discontinue investigational treatment

Medication	Washout period (before randomization)	Action (after randomization)
Systemic corticosteroids > 10 mg prednisone equivalent (until Week 16)*	2 weeks	If administered due to a medical urgency unrelated to the patient's arthritis, study treatment should be interrupted until the steroid is discontinued. If not administered for a medical urgency or for use related to the patient's arthritis, then discontinuation of investigational treatment may be required on a case by case basis
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 16)*	2 weeks	Discontinue investigational treatment (Dose adjustments allowed after Week 16) Discontinuation of investigational treatment may be required on a case by case basis.
Intra-articular corticosteroids injections (until Week 16)*	4 weeks	Discontinue investigational treatment
Intramuscular or intravenous corticosteroid treatment	4 weeks	Discontinuation of investigational treatment may be required on a case by case basis
Live vaccinations	6 weeks	If administered due to a medical urgency, study treatment should be interrupted for 4 months. If administered not for a medical urgency then discontinue investigational treatment

* See details about corticosteroid management in Section 6.2.1.
+ Regular dosing with low strength opioids is not permitted.

#In case of leflunomide treatment, a drug wash-out of 8 weeks must be performed. Another wash-out procedure might also be considered. Cholestyramine could be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40 % in 24 hours and by 49 % to 65 % in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in subjects who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days he/she can be safely randomized 4 weeks after the beginning of the 11-day treatment period.

6.2.3 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening / exacerbation of his/her disease.

Rescue medication should not be used before completion of Week 16 assessments (see Table 8-1). Although no subject will be restricted from receiving necessary rescue medications for

lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 6.2.2) occurs prior to completion of Week 16 assessments, subjects will be discontinued from study treatment and enter into the follow-up period after an end of treatment visit. Efficacy will be assessed in detail at every study visit, and subjects 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.

Changes in concomitant therapy with NSAIDs are permitted after Week 16 assessments as per investigator's clinical judgment. After Week 16, the dose and regimen of other concomitant medications may be adjusted slowly at the investigator's discretion and recorded appropriately on the CRF page.

Any use of rescue medication must be recorded in the Prior/Concomitant medications eCRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Once assigned to a subject, the Subject No. will not be reused. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At BSL visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject. The randomization number will not be communicated to any of the site staff.

Starting at Week 16, subjects who have been randomized to placebo at baseline will receive secukinumab 3 mg/kg i.v. up to Week 48. Although the investigator, site personnel and subjects are unblinded to current treatment assignment after Week 16 (as all subjects will be on secukinumab 3 mg/kg i.v starting at Week 16), original treatment assignment, as per baseline randomization, will remain blinded to the subject, investigator, and site personnel until after final database lock and analyses.

All efficacy and safety assessments should be done prior to calling IRT.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication

numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The subjects will be stratified at randomization according to disease condition (i.e. AS or nr-axSpA). Not more than 20% of randomized subjects will be TNF- IR to ensure a representative subject population for the assessment of efficacy and safety.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

This is a double-blind, randomized treatment trial.

Subjects, investigators, investigator staff and persons performing the assessments, will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst, (2) the identity of the treatments will be concealed by the use of study treatment in form of vials, filled with secukinumab or placebo that are identical in appearance.

The bioanalyst will have access to the randomization list to facilitate analysis of the PK [redacted] (i.e. to avoid the unnecessary analysis of placebo samples). Whenever needed or requested by the clinical team, the bioanalyst will share information from PK measurements before clinical database lock in a blinded fashion with the pharmacokineticist.

Starting at Week 16, subjects who have been randomized to placebo at baseline will start receiving secukinumab 3 mg/kg i.v. every four weeks up to Week 48. Although subjects, investigators, investigator staff and persons performing the assessments are unblinded to current treatment assignment after Week 16 (as all patients will be on secukinumab 3 mg/kg i.v. at Week 16), original treatment assignment, as per baseline randomization, will remain blinded to subjects, investigator staff and persons performing the assessments until after final database lock and analyses.

Unblinding will occur in the case of subject emergencies (see Section 6.6.3) and at the conclusion of the study.

Unblinding of the Global core CTT members will also occur at the time of the primary analysis database lock (see Section 12.7).

The hsCRP results from samples collected during the treatment period will be revealed to sites only after the database lock and analyses are completed. The hsCRP results from samples collected during the treatment period 1 will be revealed to Global core CTT members at the time of the primary interim analysis database lock.

6.5 Dose escalation and dose modification

Dose modifications of the investigational study drug are not permitted.

6.5.1 Dose escalation guidelines

With the proposed i.v. regimen anticipated to provide exposures of secukinumab similar to the C_{avg} and C_{max} achieved with 300 mg s.c. and C_{trough} consistently above those achieved by 150 mg s.c., dose escalations will not be provisioned for in this study.

6.5.1.1 Starting dose

The starting dose at BSL for the active arm in the study will be secukinumab 6 mg/kg. The placebo group will receive as starting dose at BSL an appropriate infusion volume matching secukinumab 6 mg/kg.

6.5.2 Dose modifications

Study treatment interruptions are not permitted with the following exceptions:

- If, in the opinion of the investigator, a subject is deemed to be placed 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 restarted at the next scheduled visit after resolution of the safety risk.
- If any prohibited medication described in Table 6-1 requires the interruption of the study treatment.

Study treatment interruptions must be recorded on the corresponding Dosage Administration Record eCRF page and all assessments should be completed as scheduled.

6.5.3 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant abnormal laboratory value, must be followed up in accordance with what is clinically indicated per the investigator until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrist, etc., should be consulted as deemed necessary.

6.5.3.1 Follow up on potential drug-induced liver injury (DILI) cases

An increase in transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potential DILI and should be considered as clinically important events.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value; subjects meeting any of the following criteria will require further follow-up as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis.

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($R > 2$ and < 5) liver injury.

In the absence of cholestasis, these subjects should be immediately discontinued from study treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, TBIL, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR, and alkaline phosphatase.

2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.

3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.

4. Obtain PK sample as close as possible to last dose of secukinumab.

5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should reported as SAE using the term "potential drug-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 6.5.2 or discontinuation of study treatment is required as described in Section 9.1.1. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

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

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with secukinumab, as detailed in pharmacokinetics section (see Section 8.5.5).

6.6.2 Recommended treatment of adverse events

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject 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 subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject 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 dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide to the subject:

- protocol number
- study drug name
- subject number

In addition, oral and written information to the subject must be provided on how to contact the investigator's backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study drug must be discontinued after emergency unblinding.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section (see Section 6.1.1).

Detailed instructions for storage, handling and administration of the study treatment are included in the Pharmacist Manual.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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

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

6.7.1.2 Handling of additional treatment

The following non-study treatment will be monitored specifically:

- Stable doses of MTX, sulfasalazine and/or NSAIDS and acetaminophen/paracetamol as applicable (see Section 6.2.1)

7 Informed consent procedures

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

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

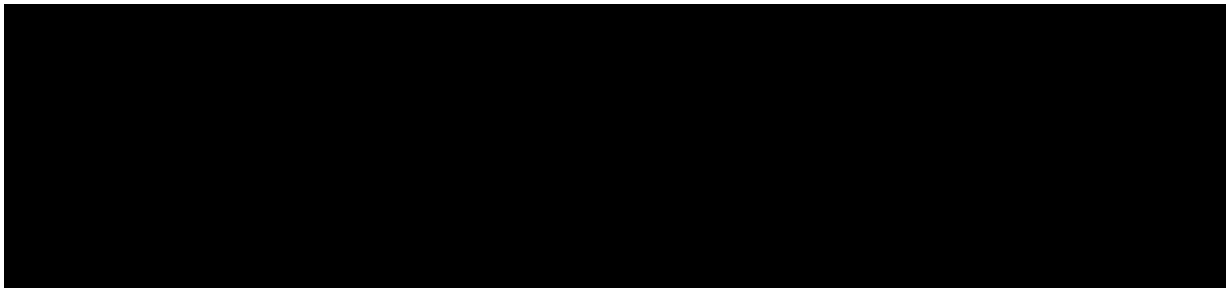
Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject

informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

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



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

Subjects will be asked to complete optional questionnaires to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible.

The study treatment should not be administered within less than 14 days after the previous administration.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for an end of treatment visit 4 weeks after the last study treatment, at which time all of the assessments listed for the final visit will be performed (corresponding to the last visit for the subject's current period of treatment (treatment period 1 or 2): i.e., Week 16 or Week 52). At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF. A follow-up visit is to be done 8 weeks after the end of treatment visit, for all subjects, regardless of whether they complete the entire study as planned or discontinue prematurely.

If they 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.

For Patient Report Outcomes (PROs) Section 16.5 provides guidance for completion of the questionnaires.

Table 8-1 Assessment Schedule

Period	Screening	Extension Screening	Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	**Screening visit 1[1]**	**Screening visit 2**	**Baseline (BSL)**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 25**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 60**
Days	**-70 to -29**	**-28 to -1**	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**175**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Informed consent	X																	
[redacted]																		
Inclusion / Exclusion criteria[2,3]	X	X	X															
Medical history/current medical conditions[2]	X	X	X															
axSpA and nr-axSpA assessment and history of extra-axial involvement[4,5]	X																	
Demography	X																	
X-ray (sacroiliac joints)[6]	X																	
MRI (sacroiliac joints)[6]		X																
Cardiovascular medical history			X															
Smoking history			X															
[redacted]																		
Physical Examination[8]		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

Period	Screening	Extension Screening	Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	**Screening visit 1[1]**	**Screening visit 2**	**Baseline (BSL)**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 25**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52**	**Week 60**
Days	**-70 to -29**	**-28 to -1**	**-**	**28**	**56**	**84**	**112**	**140**	**168**	**175**	**196**	**224**	**252**	**280**	**308**	**336**	**364**	**420**
Body Height		X																
Body Weight & BMI[9]		X	X	X	X	X	X	X	X		X	X	X	X	X	X		X
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test or QuantiFERON TB-Gold test[10]		X																
Chest X-ray or MRI[11,12]		S																
Hepatitis and HIV Screen[12,13]		S																
Hematology		X	X	X	X	X	X		X			X		X			X	X
Clinical Chemistry		X	X	X	X	X	X		X			X		X			X	X
Urinalysis		X	X	X	X	X	X		X			X		X			X	X
Pregnancy Test (serum)[14]		X																
Pregnancy test (urine)[14,15]			S	S	S	S	S	S	S		S	S	S	S	S	S	S	S
12-Lead ECG	S																	
Randomization			X															
PK blood collection			X[16]	X[16]	X[16]		X[17]		X[16]	X						X[16]	X	X
[redacted]																		
Study drug administration			X	X	X	X	X	X	X		X	X	X	X	X	X		

Period	Screening	Extension Screening	Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1[1]	Screening visit 2	Baseline (BSL)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Days	-70 to -29	-28 to -1	-	28	56	84	112	140	168	175	196	224	252	280	308	336	364	420
Prior and Concomitant Medication and Prior or Concomitant non-drug therapies/procedures	X	Update as necessary																
Wash-out evaluation / instructions	S																	
Adverse events/SAEs (including injection site reactions)[18]	X	Update as necessary																
[redacted]																		
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of back pain intensity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASFI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BASDAI			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
SF-36			X		X		X		X								X	
[redacted]																		
ASQoL			X		X		X		X								X	
[redacted]																		

Period	Screening	Extension Screening	Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1[1]	Screening visit 2	Baseline (BSL)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Days	-70 to -29	-28 to -1	-	28	56	84	112	140	168	175	196	224	252	280	308	336	364	420
[redacted]																		
PSQI			X	X	X	X	X	X								X	X	
High sensitivity C-Reactive protein (hsCRP)		X	X	X	X	X	X		X	X		X		X			X	X
HLA-B27		X																
Lipid profile[19]			X		X		X		X								X	
Cardiovascular panel			X				X		X								X	
[redacted]																		
Trial Feedback Questionnaire (TFQ)			X								X							X
Treatment period 1 completion form							X											
Treatment period 2 completion form																	X	
Follow-up completion form																		X

Period	Screening	Extension Screening	Treatment Period 1					Treatment Period 2										Follow-up
Visit Name	Screening visit 1[1]	Screening visit 2	Baseline (BSL)	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 25	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52	Week 60
Days	-70 to -29	-28 to -1	-	28	56	84	112	140	168	175	196	224	252	280	308	336	364	420

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] If the subject's washout period ≤ 4 weeks, Screening visit 1 (SV1) and Screening visit 2 (SV2) can be performed on the same day.
[2] Eligibility and relevant medical history assessments are conducted at SV1, SV2 and BSL. The data for all three visits should be recorded on the corresponding eCRFs available at SV1.
[3] A copy of the x-ray or radiologist's report must be kept in the source documentation.
[4] Extra-axial involvement such as uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis.
[5] The "modified New York criteria for AS" eCRF page will have to be completed for axSpA and nr-axSpA subjects.
[6] Only applicable for nr-axSpA subjects.
[redacted]
[8] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF. After the baseline visit, the investigator should do an abbreviated physical exam focusing on relevant clinical areas.
[9] BMI calculated at Baseline
[10] The PPD skin test can be performed at any time during the screening period, but it must be read within 72 hours and before randomization.
[11] A chest x-ray or MRI is required if it was not performed and evaluated within 3 months prior to screening. The x-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation. The x-ray may be replaced by an MRI assessment.
[12] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.
[13] 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. These assessments will be documented in source records only and will not be entered into the eCRF.
[14] Pregnancy tests will be conducted for women of child bearing potential.
[15] Kits will be provided by the central laboratory and the test is to be performed locally.
[16] At pre- and post-dose.
[17] At pre-dose.
[18] AEs / SAEs occurring after the subject has signed the informed consent must be captured on the appropriate eCRF page.
[19] Sample must be obtained fasting.
[redacted]

8.1 Screening

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration between 4 and 10 weeks, during which time the subject will sign the ICF, be evaluated for eligibility and allowed sufficient time for potential medication washout, in addition to all other assessments indicated in Table 8-1.

Screening will consist of two consecutive visits. During the first screening visit, initial assessments will be performed as outlined in Table 8-1. At that visit the duration of the washout period will be determined. The second screening visit will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to visit 2 on the same day and complete all assessments
- If the washout period is more than 4 weeks, the subject will be instructed to initiate necessary washout regimen and return for visit 2 in the next 4 weeks prior to randomization (i.e., in all cases, Visit 2 should not happen earlier than 4 weeks prior to randomization).

If subjects do not have a chest X-ray available within 3 months of screening, the X-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to radiation.The X-ray assessment may be replaced by an MRI assessment.

All subjects evaluated at visit 1 and 2 for Inclusion/Exclusion criteria should not be screen failed on the basis of a medication requiring washout, unless the subject will be unable to complete the washout in the appropriate time frame before randomization.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Section 10.1.2 for reporting details). The CRF for adverse events (AEs) should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

Subjects who are prematurely withdrawn from the study will not be replaced.

8.1.2 Re-screening

If a subject re-screens for the study, the subject must sign a new ICF and be issued a new subject number prior to any screening assessments being conducted under the new subject number. For all re-screened subjects, the investigator/qualified site staff will record if the subject was re-screened on the re-screening CRF and the original screening number the subject was issued prior to the current screening number. The date of the new informed consent signature must be entered in the Informed Consent eCRF corresponding to the new subject number. For re-screening, all screening assessments must be performed per protocol, except the tuberculosis (TB) work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected baseline date, then it is not required that the TB work up be repeated; however, the re-screened subject must repeat PPD skin test or the QuantiFERON TB-Gold performed by the central laboratory.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristics data to be collected on all subjects and to be recorded in the eCRF include:

- Age, sex, race, ethnicity and source of subject referral
- Relevant axSpA and general medical history/current medical condition data until the start of study treatment, history of extra-axial involvement (uveitis, psoriasis, inflammatory bowel disease, dactylitis, enthesitis, peripheral arthritis), number and type of previous DMARDs used, date of diagnosis of axSpA, previous axSpA therapies, functional status class according to the New York criteria, cardiovascular medical history and smoking history

Whenever possible, diagnoses and not symptoms will be recorded.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

- Assessment of SpondyloArthritis International Society (ASAS) response criteria; ASAS40, ASAS20, ASAS 5/6 and ASAS partial remission
- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- [redacted]
- Bath Ankylosing Spondylitis Functional Index (BASFI)
- Patient's global assessment of disease activity (VAS)
- Patient's assessment of back pain intensity (VAS)
- [redacted]
- Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)
- Ankylosing Spondylitis Quality of Life (ASQoL)
- High sensitivity C-Reactive Protein (hsCRP)
- [redacted]

[redacted]

- Ankylosing Spondylitis Disease Activity Score (ASDAS)-C-Reactive Protein (CRP) and ASDAS response categories

[redacted]

- Sleep improvement ([redacted] sleep PROs)

8.3.1 Assessment of SpondyloArthritis International Society criteria (ASAS)

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

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

[redacted]

2. C-reactive protein (acute phase reactant)

8.3.1.1 ASAS Response Criteria-40% (ASAS40)

ASAS40 response is defined as a ≥40% improvement and an absolute improvement from baseline of ≥20 units (range 0–100) in ≥ 3 of the following 4 domains: back pain [10 cm visual analogue scale (VAS)], patient global assessment of disease activity (10 cm VAS), physical function (BASFI; range 0–100) and inflammation (mean score of items 5 and 6 of the BASDAI; both 10 cm VAS) without any worsening in the remaining domain.

8.3.1.2 ASAS Response Criteria-20% (ASAS20)

The ASAS Response Criteria (ASAS20) is defined as an improvement of ≥20% and ≥1 unit on a scale of 10 in at least three of the four main domains and no worsening of ≥20% and ≥1 unit on a scale of 10 in the remaining domain.

8.3.1.3 ASAS 5/6 improvement criteria

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

8.3.1.4 ASAS partial remission criteria

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

8.3.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

1. Fatigue
2. Spinal pain
3. Peripheral joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

To give each symptom equal weight, the mean (average) of the two scores relating to morning stiffness is taken into account (questions 5 and 6). The resulting 0 to 10 score is added to the scores for questions 1 through 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 the disease and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or 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.

[redacted]

8.3.4 Bath Ankylosing Spondylitis Functional Index (BASFI)

The Bath Ankylosing Spondylitis Functional Index is a set of 10 questions designed to determine the degree of functional limitation in subjects with AS. The questions were chosen on the basis of predominant input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

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

The patient's global assessment of disease activity will be performed using a 100 mm VAS ranging from none to very severe in response to the question *"How active was your disease on average during the last week?*".

8.3.6 Patient's assessment of back pain intensity (VAS)

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

[redacted]

8.3.8 Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)

The Medical Outcome Short Form Health Survey is a widely used and extensively studied instrument to measure health-related quality of life among healthy patients and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health (Ware and Sherbourne 1992). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (McHorney et al 1993). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual patients.

The purpose of the SF-36 in this study is to assess the health-related quality of life (HRQoL) of patients. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

8.3.9 Ankylosing Spondylitis Quality of Life (ASQoL)

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

The purpose of the ASQoL is to assess the disease specific QoL of patients in this study.

8.3.10 High Sensitivity C-reactive protein (hsCRP)

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

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

[redacted]

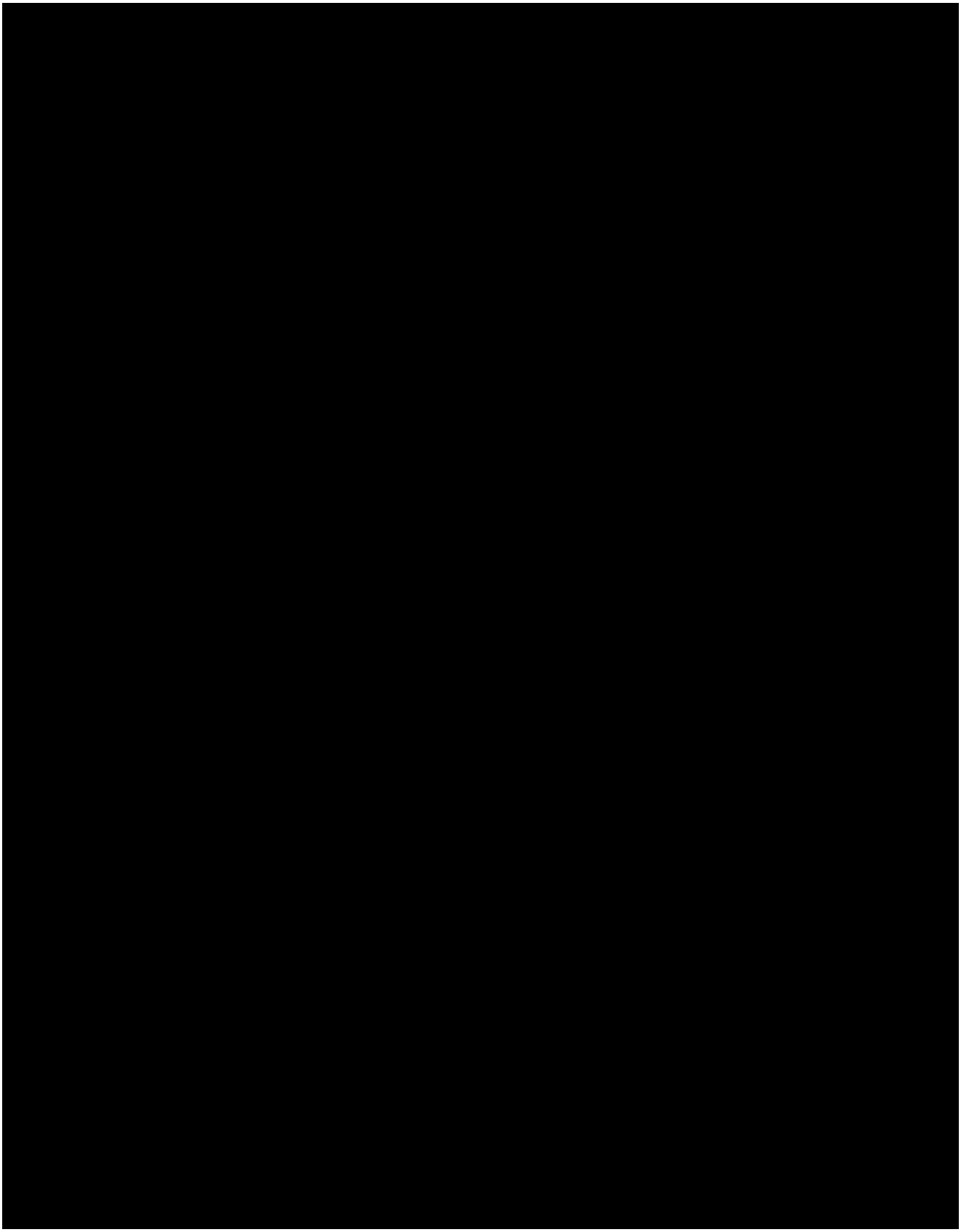
8.3.13 ASDAS-CRP and ASDAS response categories

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a composite index to assess disease activity in AS.

ASDAS-CRP will be utilized to assess the disease activity status. Parameters used for the ASDAS include: total back pain (BASDAI question 2), the patient global assessment of disease activity, peripheral pain/swelling (BASDAI question 3), duration of morning stiffness (BASDAI question 6) and C-reactive protein (CRP) in mg/L (Lukas et al 2009).

Disease activity states: 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 cutoffs for improvement scores are a change ≥1.1 unit for "minimal clinically important improvement" and a change ≥2.0 units for "major improvement" (Machado et al 2011).

[redacted]



8.3.16 Sleep improvement

To measure improvement in sleep and reduction in nocturnal awakening, subjective sleep PROs [redacted] Pittsburg Sleepness Quality Index; PSQI) will be used [redacted]

[redacted]

8.3.16.2 Sleep PROs

Patients with AS also report chronic and extensive sleep disturbance due to pain and stiffness during the night (Leverment et al 2017). Often patients get out of bed and walk around during the night to reduce pain and stiffness, which can lead to daytime fatigue (Rudwaleit et al 2006). In patients with AS, poor quality sleep is strongly correlated with increased pain, lower quality of life, higher depressed mood, higher disease activity and reduced physical function (Batmaz et al 2013). Additionally, there is a general lack of data to investigate associations between sleep disturbance and daytime fatigue levels in AS.

To study the effect of secukinumab on AS related sleep disturbance, the subjective sleep PRO's in Section 8.3.16.2.1 and Section 8.3.16.2.2 will be used.

[redacted]

8.3.16.2.2 Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index is a self-report questionnaire that assesses sleep quality over a 1-month time interval. Consisting of 19 items, the PSQI measures several different aspects of sleep, offering seven component scores and one composite score. The component scores consist of subjective sleep quality, sleep latency (i.e., how long it takes to fall asleep), sleep duration, habitual sleep efficiency (i.e., the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction.

Each item is weighted on a 0–3 interval scale. The global PSQI score is then calculated by totaling the seven component scores, providing an overall score ranging from 0 to 21, where lower scores denote a healthier sleep quality.

The PSQI is self-administered and to be completed as per the assessment schedule on an electronic device.

8.3.17 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are standard measures used across all axSpA trials and are required for regulatory filing.

8.4 Safety

Evaluation of all AEs and SAEs including injection site reactions, electrocardiograms (ECGs), physical examination, vital signs and laboratory assessments will occur. [redacted]

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test or PPD skin test
- Hepatitis and human immunodeficiency virus (HIV) screen
- Laboratory evaluations (Hematology, clinical chemistry, lipid panel, cardiovascular panel, urinalysis and pregnancy test)
- Evaluation of AE/ SAE's
- Electrocardiogram
- Local tolerability (Injection site reactions)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- [redacted]

Table 8-3 Assessments & Specifications

Assessment	Specification

Physical	A complete physical examination of the subject will be performed according to the schedule defined in Table 8-1 and will include the examination of general appearance, hydration status, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent form must be recorded on the appropriate CRF that captures medical history screen on the patient CRF. Significant findings that occur after signing informed consent form which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.
Height and weight	Height in centimeters (cm) and body weight, to the nearest 0.1 kilogram (kg), in indoor clothing but without shoes, will be measured. If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

8.4.1 QuantiFERON TB-Gold test or PPD skin test

Either a QuantiFERON TB-Gold test **or** a PPD skin test must be performed at screening visit 2. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines), establishes conclusively that the subject has no evidence of active tuberculosis, OR, if presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated prior to enrollment.

8.4.1.1 A QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second screening visit and the results to be known prior to randomization to determine the subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection.

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.

8.4.1.2 PPD skin test

A PPD skin test is to be performed at screening and read before randomization to determine the subject's eligibility for the trial, if a QuantiFERON test is not performed. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration), will take 48-72 hours to develop, the subjects must return to the study site within that time for evaluation of the injection site. This will determine whether the subject has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm (or according to local practice/guidelines) is interpreted as a positive result.

8.4.2 Hepatitis and human immunodeficiency virus (HIV) screen

Screening for hepatitis and HIV is optional, based on the judgment of the investigator or if required by local regulations. If hepatitis testing is performed, testing will include hepatitis B surface antigen (HBsAg) and anti-HCV antibodies. If HIV testing is performed, positive HIV screening will be confirmed by a second technique available at the respective local laboratory, e.g., Western blot.

8.4.3 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Section 16.1. All subjects 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.

Table 8-4 Specifications of Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, platelets, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.
Chemistry	Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorus, total protein, albumin, and uric acid.
Urinalysis	Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood, and WBCs will be recorded in the appropriate eCRF.

Lipid Panel	A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), total cholesterol, and triglycerides will be measured from a fasting blood sample.
Cardiovascular panel	A cardiovascular profile including lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be done from a blood sample.
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' section)

8.4.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 8-1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection followed by vital signs and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings must be discussed with the sponsor before randomization of the subject into the study.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.5 Local tolerability (Injection site reactions)

Local tolerability at the site of i.v. injection of the study treatment will be assessed in case of any local reaction, and followed up until this has disappeared**.**

The assessment of pain, redness, swelling, induration, hemorrhage and itching, including severity (mild, moderate, severe) and duration, will be performed by a physician and will be recorded on the Adverse Events eCRF.

8.4.6 Pregnancy and assessments of fertility

The study treatment must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

A serum β-hCG test will be performed in all women at screening. All women who are not surgically sterile or post-menopausal (as defined in Section 5.2) at screening will have local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must discontinue study treatment.

8.4.7 Tolerability of secukinumab

Tolerability will be assessed by adverse events, laboratory values, injection site reaction [redacted].

8.4.9 Other safety evaluations

Chest X-ray or MRI

A chest X-ray or MRI at screening visit 2 (except for subjects who have a valid chest X-ray or MRI done within 3 months prior to screening) is performed to rule-out the presence of a pulmonary malignancy or infectious process, in particular, tuberculosis.

8.4.10 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 or MRI at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy or infectious process, in particular, pulmonary tuberculosis. The radiation exposure that results from the chest X-ray safety measurements are estimated to be far below 1 mSv (millisievert). For effective radiation doses under 3 mSv (300 mrem; 300 milliroentgen equivalent man), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure adequate safety measures before the treatment with a biologic.

The safety assessments selected are standard and adequate for this indication/subject population.

8.5 Additional assessments

The other assessments planned for the study are:

- Quality of Life questionnaires/ Patient reported outcomes (PROs)
- Trial Feedback Questionnaires
- [redacted]
- HLA-B27
- Pharmacokinetics
- [redacted]
- Activity/Mobility improvement
- Sacroiliac Joint X-ray
- Sacroiliac Joint MRI

[redacted]

8.5.2 Trial Feedback Questionnaires

This trial will include an anonymized questionnaire, 'Trial Feedback Questionnaire' for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be reported to the investigator.

8.5.4 HLA-B27

A blood sample to analyze Human leukocyte antigen B27 (HLA-B27) will be obtained from all subjects as indicated in Table 8-1.

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

8.5.5 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the visits defined in the assessment schedule (Table 8-1) and Table 8-3.

All blood samples will be drawn by direct venipuncture in a forearm vein.

The actual sample collection date and exact time will be entered on the PK blood collection summary eCRF. The reason for not taking blood samples will be captured in the eCRF.

The bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the PK samples. The bioanalyst will provide the samples' concentration data to the team under blinded conditions. Bioanalyst will keep this information blinded until the interim clinical database lock.

PK sample handling, labeling and shipment instructions:

Laboratory manuals will be provided by the central laboratory with detailed information on sample collection, sample handling and shipment.

Tubes and labels will be provided by the central laboratory with study/sample type information pre-printed on the label.

Table 8-6 PK sample log

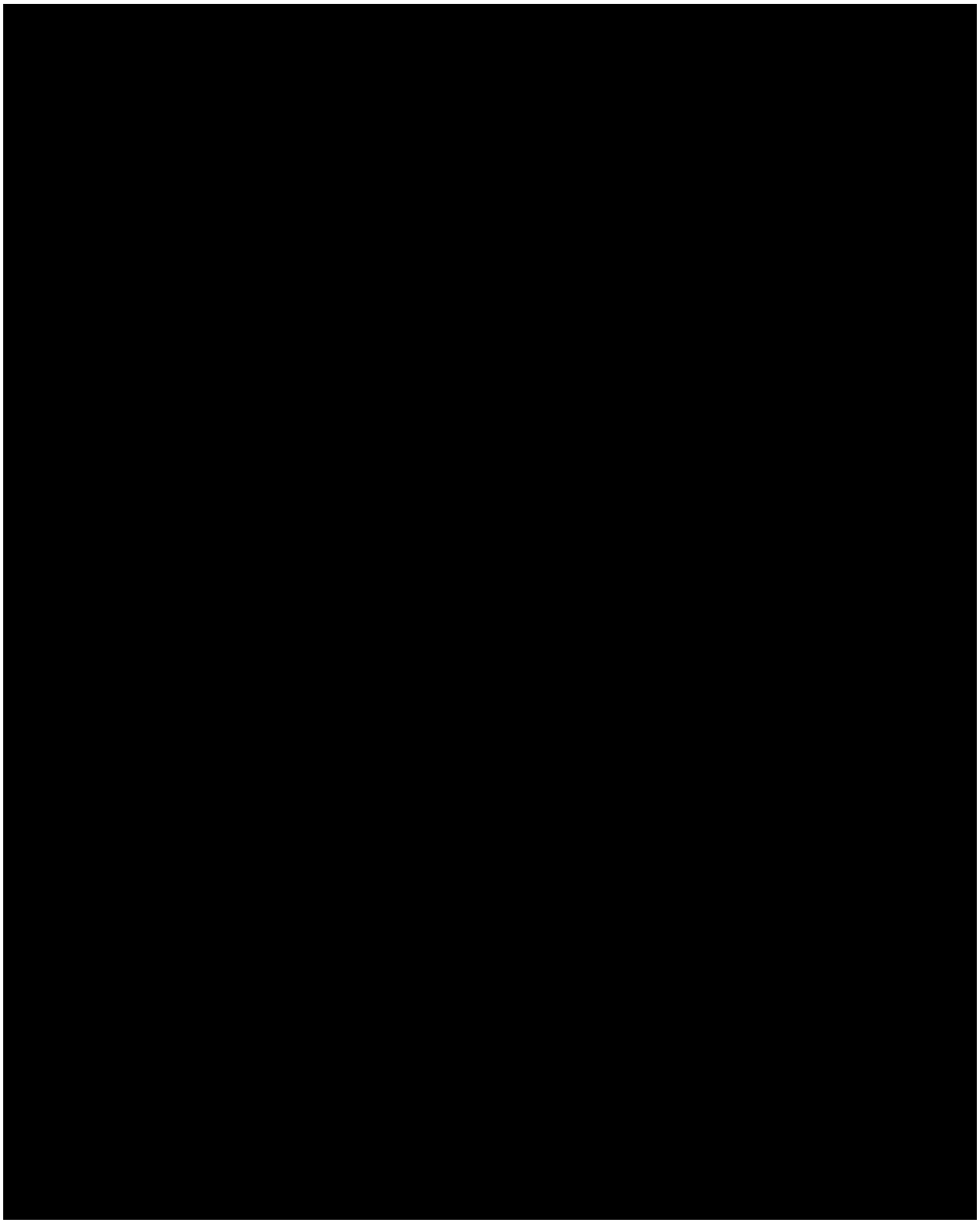
Week	Timepoint	PK sample number*	PK collection number
BSL	0 h (pre-dose)	1	1
BSL	0.5 h	2	1
Week 4	0 h (pre-dose)	3	2
Week 4	0.5 h	4	2
Week 8	0 h (pre-dose)	5	3
Week 8	0.5	6	3
Week 16	0 h (pre-dose)	7	4
Week 24	0 h (pre-dose)	8	5
Week 24	0.5 h	9	5
Week 25	anytime	10**	5
Week 48	0 h (pre-dose)	11	6
Week 48	0.5 h	12	6
Week 52	anytime	13**	6
Week 60	anytime	14**	6

* If a PK sample is collected at an unschedule visit, the sample number will follow the pattern: 1001, 1002, etc.
** Post-dose time point for sample number 10 refers to the dose given at Week 24. Post-dose time points for sample numbers 13 and 14 refer to the last dose given at Week 48.

PK analytical methods

An ELISA method will be used for the bioanalytical analysis of AIN457 in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. The detailed method description to assess the Secukinumab concentration will be described in the Bioanalytical Data Report (BDR).

Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the BDR.



[redacted]

8.5.7 Activity/Mobility improvement

This study will also investigate the association between treatment with i.v. secukinumab and daytime activity patterns by using relevant components of PRO's (BASDAI, [redacted] amongst others) [redacted]

8.5.8 Sacroiliac Joint X-ray

For eligibility purpose, an SIJ X-ray will be obtained from nr-axSpA as defined in the assessment schedule (Table 8-1) and according to the imaging acquisition guidelines provided by the central imaging laboratory. The X-ray images should be transferred to the central imaging laboratory following acquisition. The central imaging laboratory will conduct independent review for all sacroiliac X-rays in this trial to determine eligibility of patients with nr-axSpA.

8.5.9 Sacroiliac Joint MRI

For eligibility purpose, an SIJ MRI will be obtained from nr-axSpA subjects as defined in the assessment schedule (Table 8-1) and according to the imaging acquisition guidelines provided by the central imaging laboratory. The MRI images should be transferred as anonymized electronic files to the central imaging laboratory following acquisition. The central imaging laboratory will conduct independent review for all sacroiliac MR imaging in this trial.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent (WoC)
- Emergence of the following adverse events:

  a. Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable 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
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Section 16.1.)
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any protocol deviation that results in a significant risk to the subject’s safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if there is a lack of improvement or worsening of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the subject's well-being.

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' Section 9.1.2). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up Section 9.1.3. This contact should preferably be done according to the study visit schedule.

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

Subjects who prematurely discontinue or withdraw during a specific treatment period should return, 4 weeks after the last study treatment, for the final visit within that treatment period (i.e., Week 16 for treatment period 1 or Week 52 for treatment period 2), as well as return for the follow-up visit (i.e.,Week 60) 12 weeks after the last study treatment, see Table 8-1. The final visit should be performed before any new treatment is initiated.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code Section 6.6.3.

9.1.1.1 Replacement policy

Subjects who are prematurely withdrawn from the study will not be replaced by newly enrolled subjects.

9.1.2 Withdrawal of informed consent

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

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

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

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

Further attempts to contact the subject 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 subject's study withdrawal should be made as detailed in the assessment table.

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

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

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

9.1.3 Lost to follow-up

For subjects 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 subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until his/her scheduled end of study visit would have been occured.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

A subject will be considered to have completed the study if he/she received a maximum of 52 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including visit Week 60.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation will be recorded on the appropriate Study Phase Completion eCRF page.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing medical care. This medical care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

If, at study completion, the investigator determines that a patient could benefit from continued secukinimab treatment, the physician may request access from Novartis, at no cost to the patient, if not commercially available and accessible.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of

underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject

3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

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

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

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events 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 subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

10.1.2 Serious adverse events (SAEs)

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject 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 the ICH-E2D Guidelines).

- 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
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
    - 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
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Any SAEs experienced from the 30 day period after the last study visit only reported to Novartis if the investigator suspected 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 reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event 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 of each SAE to study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements on investigator's signature can be found in the investigator folder provided to each site.

If the SAE is previously not documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (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.

10.1.4 Pregnancy reporting

Pregnancies

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

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject 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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject 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 two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Section 16.6 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case

of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Investigations which can be based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 27,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests resulting in clinically significant abnormal values (see Section 16.1 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

Once all the necessary 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/moved to restricted area to be accessed byindependent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis 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 GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, 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.

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

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 subjects will be disclosed.

12 Data analysis and statistical methods

The primary endpoint analysis will be performed after all subjects complete Week 16 as described in Section 12.7 and the final analysis will be conducted on all subject data at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will generally include the number of subjects (N), minimum, lower quartile, mean, standard deviation (SD), median, upper quartile, and maximum. For categorical or binary variables, the number and percent of subjects in each category will be presented. P-values presented will be two-sided unless otherwise specified.

Inferential efficacy comparisons with placebo will be performed on the first 16 weeks of treatment.

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

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

- Secukinumab i.v. regimen
- Placebo regimen

Note that the treatment groups above for a subject may differ depending on the time period of the analysis and whether one assesses the subject for efficacy or safety (see Section 12.1 for details).

12.1 Analysis sets

The following analysis sets will be used in this study:

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

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be evaluated according to the treatment assigned to at randomization.

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

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

The following common background and demographic variables will be summarized:

- Gender, age, race, ethnicity, weight, height, and BMI.

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

- Patient's global assessment of disease activity and other ASAS components, hsCRP (mg/L and >ULN), [redacted], prior use (yes/no) of TNF-alpha inhibitors, use (yes/no) and separate dose of MTX (mg/week), sulfasalazine (g/day) and systemic corticosteroids (mg/day) at randomization, time since first diagnosis of axSpA (years), modified New York criteria for AS, HLA-B27, [redacted], total back pain (VAS), nocturnal back pain (VAS), total BASDAI score, spinal pain (BASDAI question #2) [redacted].

Medical history

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

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

12.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of visits with active and placebo i.v. infusions received will be presented by treatment group.

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

Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

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

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

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

The number and percentage of subjects receiving prior and concomitant axSpA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to axSpA therapies previously. [redacted]

12.4 Analysis of the primary endpoint(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 12.5.1.

12.4.1 Definition of primary endpoint(s)

The primary efficacy variable is response to treatment according to the ASAS40 criteria at Week 16 in patients with active axSpA (AS and nr-axSpA). The analysis of the primary variable will be based on the FAS population.

12.4.2 Statistical model, hypothesis, and method of analysis

The estimand for primary endpoint is defined as follows:

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

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

C. Intercurrent event: the intercurrent event is captured through the variable definition

D. Population-level summary: difference in proportions of responders between the secukinumab and placebo arms

The statistical hypothesis for ASAS40 being tested is that there is no difference in the proportion of subjects fulfilling the ASAS40 criteria at Week 16 in the secukinumab i.v. regimen versus placebo regimen.

Let p_0 denote the proportion of ASAS40 responders at Week 16 for placebo regimen and p_1 denote the proportion of ASAS40 responders at Week 16 for secukinumab i.v. regimen.

In statistical terms, H_1: $p_1 = p_0$, H_{A1}: $p_1 \neq p_0$, i.e.,

> H_1: secukinumab i.v. regimen is not different to placebo regimen with respect to ASAS40 response at Week 16

The primary analysis will be conducted via logistic regression with treatment and stratification factor (disease condition) as factors and weight as a covariate. Difference in marginal response proportions with p-value and 95% confidence interval (CI) will be presented comparing secukinumab i.v. regimen to placebo.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data for ASAS40 response and other binary efficacy variables (e.g., ASAS 5/6, etc.) for data up to Week 16 will be handled as follows:

1. Patients who drop out of the trial for any reason will be considered as non-responders from the time they drop out through Week 16
2. Patients who do not have the required data to compute responses (e.g., ASAS components) at baseline and at the specific timepoint will be classified as non-responders at the specific timepoint.

Patients who are unblinded prior to the scheduled time point will be considered non-responders from the time of unblinding up to Week 16. The primary analysis will use the non-responder imputation.

Continuous variables (e.g., ASAS components) will be analyzed using a mixed-effects model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption. As such, single-point imputation of missing data will not be performed (e.g., LOCF). For analyses of these parameters, if all post-baseline values are missing then these missing values will not be imputed and this patient will be removed from the analysis of the corresponding variable, i.e., it might be that the number of patients providing data to an analysis is smaller than the number of patients in the FAS.

12.4.4 Sensitivity and Supportive analyses

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

In order to determine the robustness of the logistic regression model used for the primary analysis, ASAS40 response at Week 16 will also be evaluated using a non-parametric ANCOVA model (Koch et al 1998) with the same independent variables as the logistic regression model. In addition, further logistic regression models may be conducted which explore the impact of other baseline or disease characteristics (and respective interactions with treatment group) on response.

The impact of missing data on the analysis results of ASAS40 will be assessed as well by repeating the logistic regression model using different ways to handle missing data.

These may include, but are not limited to:

- Multiple imputation
- Observed data analysis
- Tipping point analysis

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy variables and the method for adjusting for multiplicity are described below. Secondary efficacy variables will be analyzed using the FAS population. Handling of missing data for secondary variables included in the testing strategy will be the same as for the primary variable.

Estimand definition for the secondary variables

Estimand definition for the secondary binomial variables (e.g., ASAS 5/6, etc.) is the following:

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

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

C. Intercurrent event: the intercurrent event is captured through the variable definition

D. Population-level summary: difference in proportions of responders between the treatment conditions

The estimand of binary variables is (secukinumab vs placebo) obtained from a logistic regression model at week 16 in the FAS population. In the analysis, patients dropping out or being unblinded before week 16 or having missing response data at week 16 are considered as non-responders.

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

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

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

C. Intercurrent event: had no intercurrent events occured before week 16

D. Population-level summary: difference in variable means between the treatment conditions

The estimand of continuous variables at week 16 is (secukinumab vs placebo) obtained from MMRM in the FAS population assuming patients dropping out or having missing data at week 16 are missing-at-random. MAR imputation will be implemented through an MMRM or multiple imputation model.

ASDAS-CRP major improvement at Week 16

Response at Week 16 to ASDAS-CRP major improvement criteria will be evaluated using a logistic regression model with treatment, stratification factor (disease condition) as factors and weight and baseline score as a covariate.

BASDAI at Week 16

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

ASAS 5/6 at Week 16

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

BASFI at Week 16

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

SF-36 PCS at Week 16

See Section 12.5.7 Patient Reported Outcomes.

ASQoL at Week 16

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

hsCRP at Week 16

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

ASAS20 at Week 16

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

ASDAS-CRP inactive disease at Week 16

Response at Week 16 to ASDAS-CRP inactive disease criteria will be evaluated using a logistic regression model with treatment, stratification factor (disease condition) as factors and weight and baseline score as a covariate.

ASAS partial remission at Week 16

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

PSQI at Week 16

Summary statistics of observed data by visit and change from baseline in total PSQI score will be provided for each treatment regimen. Between-treatment differences will be evaluated using MMRM. Treatment group, stratification factor (disease condition) and analysis visit will be included as categorical factors and baseline PSQI scores and weight as continuous covariates. Treatment by analysis visit and baseline PSQI scores by analysis visit will be included as

interaction terms in the model. An unstructured covariance structure will be assumed for the model.

Testing Strategy

The following null hypotheses will be included in the testing strategy, and type-I-error will be set such that a family-wise type-I-error of 5% is kept:

Primary objective:

H_1: secukinumab i.v. regimen is not different to placebo regimen with respect to signs and symptoms (ASAS40 response) in axSpA patients at Week 16

Secondary objectives:

H_2: secukinumab i.v. regimen is not different to placebo regimen with respect to ASDAS-CRP major improvement in axSpA patients at Week 16

H_3: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in total BASDAI in axSpA patients at Week 16

H_4: secukinumab i.v. regimen is not different to placebo regimen with respect to ASAS 5/6 response in axSpA patients at Week 16

H_5: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in BASFI in axSpA patients at Week 16

H_6: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in SF-36 PCS in axSpA patients at Week 16

H_7: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in ASQoL in axSpA patients at Week 16

H_8: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in hsCRP in axSpA patients at Week 16

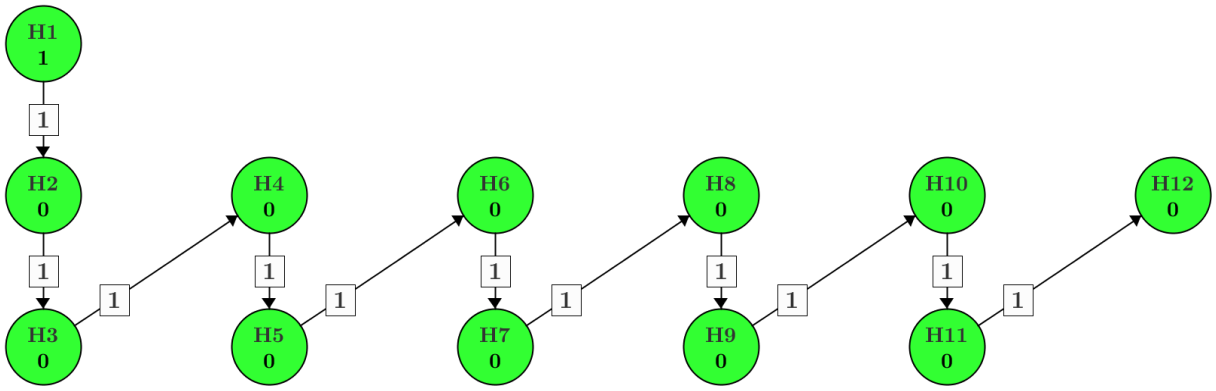
H_9: secukinumab i.v. regimen is not different to placebo regimen with respect to ASAS20 response in axSpA patients at Week 16

H_{10}: secukinumab i.v. regimen is not different to placebo regimen with respect to ASDAS-CRP inactive disease in axSpA patients at Week 16

H_{11}: secukinumab i.v. regimen is not different to placebo regimen with respect to ASAS partial remission in axSpA patients at Week 16

H_{12}: secukinumab i.v. regimen is not different to placebo regimen with respect to change from baseline in PSQI in axSpA patients at Week 16

Figure 12-1 Testing strategy



The family-wise error will be set to α=5% and it will be controlled with the proposed sequential testing strategy as described in Figure 12-1. The primary hypothesis (H_1) for the primary objective (ASAS40 at Week 16) for secukinumab i.v. regimen versus placebo will be tested at α-level. If the hypothesis H_1 is rejected then the whole α will be passed to the next hypothesis (H_2) which will be tested at α-level. This procedure will continue (pending rejection of the null hypotheses) until H_{12} is rejected.

Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the sequence for the test of another hypothesis if the treatment effect is in favor of secukinumab.

12.5.2 Safety endpoints

Adverse events

Treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

As appropriate, the incidence of AEs will be presented per 100 subject years of exposure (exposure-adjusted incidence rates).

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

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

When adjudication is required of major cardiovascular events, a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline.

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a subject's baseline laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post-baseline.

[redacted]

[redacted]

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 subjects with both baseline and post-baseline values.

12.5.3 Pharmacokinetics

All subjects with concentration data will be included in the PK data analysis.

Pharmacokinetic variables

The following PK parameter will be determined: Cmin,ss. Cmin,ss will be determined using Phoenix software. Individual serum concentrations in µg/mL will be listed. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantification will be treated as zero in summary statistics for concentration data only.

During modeling of the PK of secukinumab, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed.

Statistical methods for pharmacokinetic analyses

Summary statistics by visit/time will be provided for the above mentioned parameter and will include arithmetic and geometric means, SD, median, minimum and maximum. Individual concentrations will be listed by subject.

12.5.7 Patient Reported Outcomes (PROs)

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

BASDAI

The following variables will be evaluated:

- BASDAI
- [redacted]

For BASDAI, see Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s) for details.

[redacted]

BASFI

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s).

[redacted]

Patient's assessment of back pain intensity (VAS)

Summary statistics of observed data by visit and change from baseline in patient's assessment of back pain intensity will be provided for each treatment.

SF-36

The following variables will be evaluated:

- SF-36 domain scores (based on a scale of 0-100)
- SF-36 PCS [redacted] (norm-based scores)
- SF-36 PCS [redacted] (improvement of ≥ 2.5 points, Lubeck 2004)

For the change in SF-36 summary scores (PCS [redacted]), summary statistics will be provided using observed data for each treatment regimen.

For the responder analyses, the proportion of responders will be descriptively summarized along with its 95% CI for each randomized treatment based on observed data.

The SF-36 domain scores will be summarized by treatment.

ASQoL

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s).

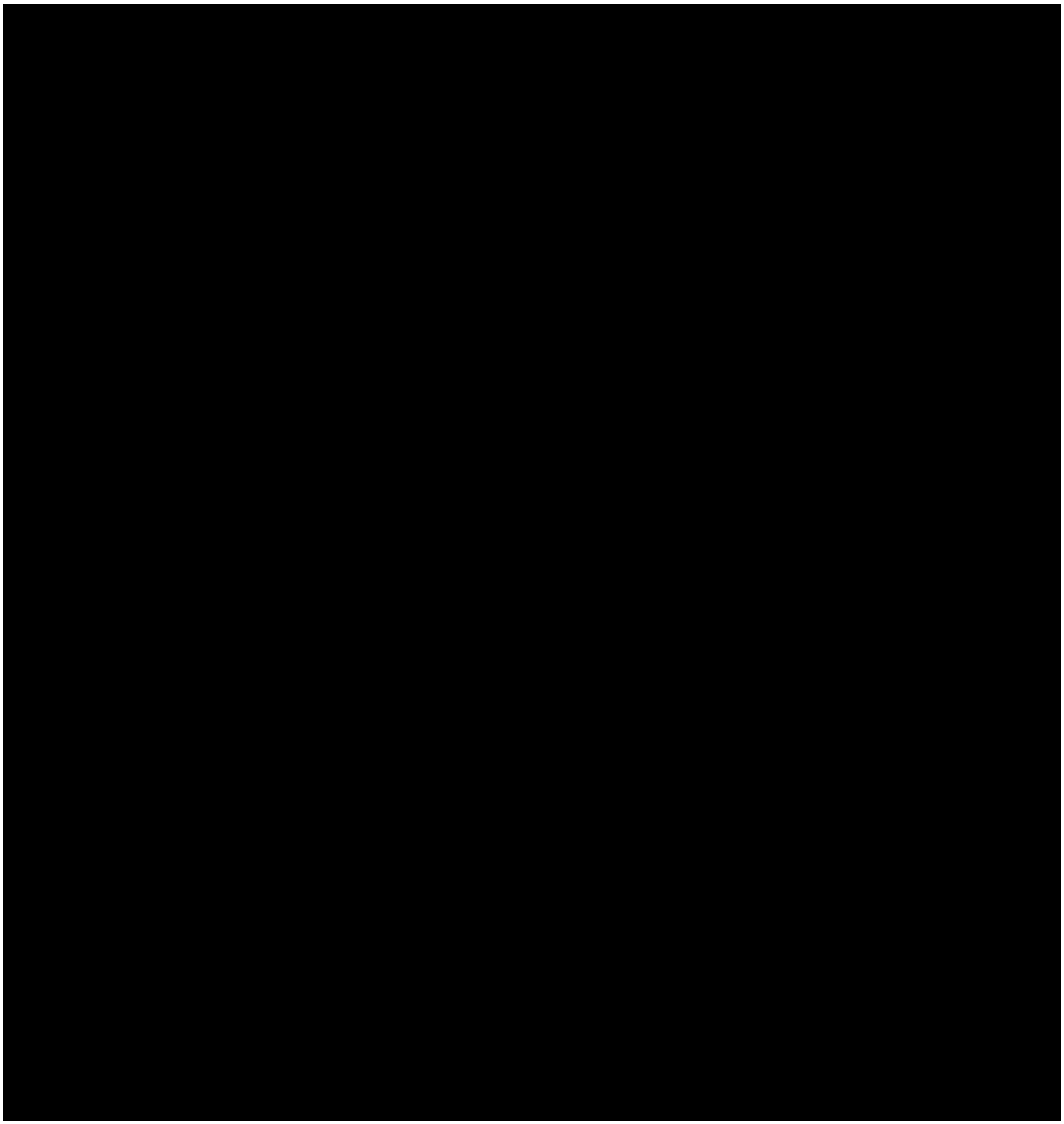
[redacted]

[redacted]

PSQI

See Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s).

[redacted]



The secukinumab i.v. regimen will be compared for primary and secondary variables as part of the regular statistical models (e.g., logistic regression and MMRM).

For binary variables, the proportion of responders for these endpoints (e.g., achieving ASAS20) may be summarized along with its 95% CI for each randomized treatment based on observed data. Details will be provided in the statistical analysis plan.

Between-treatment comparisons for binary variables in the FAS population (e.g., ASAS20, ASAS40, ASDAS inactive disease, etc.) at individual analysis visits will be evaluated in a logistic regression model with treatment group, stratification factor (disease condition) as factors and baseline score (if appropriate) and weight as covariates. Difference in marginal

response proportions with p-value and 95% CI will be presented for treatment comparison up to Week 16.

For continuous variables, summary statistics may be provided for the variables using the observed data or change from baseline for each treatment regimen. Summary statistics include N, mean, SD, minimum, lower quartile, median, upper quartile and maximum. Details will be provided in the statistical analysis plan.

Continuous variables (e.g., change from baseline in ASDAS) will be evaluated using MMRM with treatment regimen, stratification factor (disease condition) and analysis visit as factors and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. Variables such as hsCRP whose distribution is not anticipated to be normal will be transformed and analyzed on the $\log_e$ scale and back transformed prior to presentation.

12.7 Interim analyses

The primary endpoint analysis will be performed after all subjects complete Week 16 in order to support regulatory filing. As the primary analysis is scheduled at Week 16, no adjustment will be made to the testing strategy to control family-wise type I error rate for this analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

An overall type I error (2-sided) of 5% will be used to control type I error. Secukinumab i.v. regimen will be tested versus placebo with respect to the primary endpoint (ASAS40 response at Week 16). A sample size of 250 axSpA patients (200 AS patients and 50 nr-axSpA patients) per group is deemed appropriate to achieve adequate power for the primary and secondary endpoints for this study.

An ASAS40 response rate of about 28.2% for the AS population in the placebo group at week 16 was reported in a published phase III study (CAIN457F2320). The ASAS40 response to secukinumab 150 mg is estimated to be 44.9% in the AS population based on the lower bound of the 90% confidence interval of risk difference from the meta-analysis of 3 phase III studies (CAIN457F2310, CAIN457F2320 and CAIN457F2308). With 250 patients per treatment group (200 AS patients and 50 nr-axSpA patients), there would be approximately 96% power to detect a treatment difference of 16.7% in ASAS40 response rates between secukinumab and placebo in the evaluation of the primary efficacy hypothesis at Week 16 (Chi Square test, NQuery 7.0). The overall sample size will be 500 patients (400 AS patients and 100 nr-axSpA patients) for a randomization ratio of 1:1.

12.8.2 Secondary endpoint(s)

The estimated power with the chosen sample size for secondary efficacy endpoints based on the pooled results of the same phase III studies (CAIN457F2310, CAIN457F2320 and CAIN457F2308) are summarized in Table 12-1 for binary endpoints and Table 12-2 for continuous endpoints.

Table 12-1 Summary of power for binary secondary endpoints

Endpoint	Response Rate		Power
	Secukinumab(N = 200 AS + 50 nr-axSpA)	Placebo (N = 200 AS + 50 nr-axSpA)	
ASAS 5/6	44.2%	19.5%	99%
ASDAS-CRP major improvement	27.8%	6.4%	99%
ASAS20	59.0%	38.4%	99%
ASDAS-CRP inactive disease	13.6%	3.5%	97%
ASAS partial remission	15.2%	5.5%	92%

Table 12-2 Summary of power for continuous endpoints

Endpoint	Mean change from baseline		Common standard deviation	Power
	Secukinumab(N = 200 AS + 50 nr-axSpA)	Placebo (N = 200 AS + 50 nr-axSpA)		
hsCRP[1]	-0.79	0.09	0.867	99%
BASDAI	-2.61	-1.48	2.241	99%
BASFI	-2.14	-1.13	2.253	99%

SF-36 PCS	6.87	3.99	6.898	99%
ASQoL	-4.46	-2.56	4.714	99%
PSQI[2]	-1	0	3.9	81%

[1] hsCRP is in log scale
[2] Source: mean change from baseline is from Karatas et al 2018 (AS study, median was used) and common standard deviation is from Taylor-Gjevre et al 2011 (RA study, largest standard deviation was used).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

15 References

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

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

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

Table 16-1 Safety Analyses: Expanded Limits and Notable Criteria

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

HEMATOLOGY VARIABLES

Hemoglobin: 20 g/L decrease from baseline

Platelet count: <100x10E9/L

White blood cell count: <0.8 x LLN

Neutrophils: <0.9 x LLN

16.2 Appendix 2: Modified New York criteria

Clinical criteria:

· 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

· Sacroiliitis grade ≥2 bilaterally or grade 3–4 unilaterally.

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

16.3 Appendix 3: ASAS, BASFI [redacted]

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

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

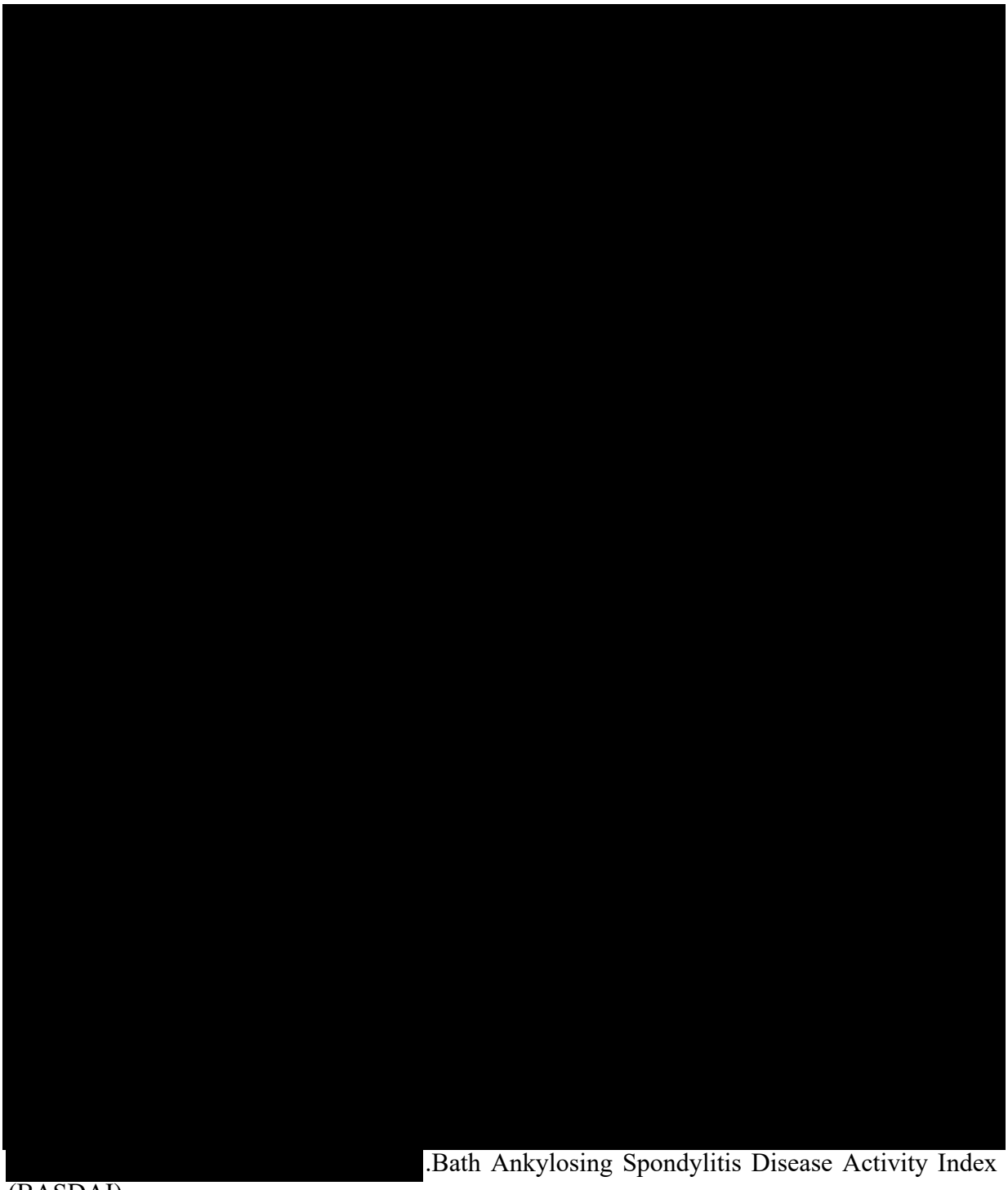
Additional assessment domains:

[redacted]

2. C reactive protein (acute phase reactant)Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 10cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.[redacted]

[redacted]



.Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

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

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?
2. How would you describe the overall level of AS **neck, back or hip pain** you have had?

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

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0 to 10 number is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at Ankylosing Spondylitis. BASDAI is a quick and simple index (taking between 30 seconds and 2 minutes to complete.

16.5 Appendix 5: Guidelines for administering the PRO questionnaires

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

All questionnaires will be completed on an electronic device at the scheduled study visit prior to the subject seeing the investigator for any clinical assessment or evaluation. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaire. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses. A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses that may indicate potential adverse events (AEs) or serious adverse events (SAEs). The investigator should review not only the responses to the questions in the questionnaires, but also any unsolicited comments written by the subject. If AEs or SAEs are confirmed, then the physician must record the events. Investigators should not encourage the subjects to change the responses reported in the completed questionnaires.

The language in which each of the questionnaires to be completed will also be captured the first time a questionnaire is administered.

Before trial begin

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a subject's response might highlight issues of potential concern. *For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a subject responds 'most or all of the time', then the study coordinator should inform the study investigator.*

Before completion

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

During completion

1. Administrator may clarify the questions but should not influence the response

2. Only one response for each question
3. Also see 'Addressing Problems and Concerns'

After completion

1. Check for completeness and not for content*
2. Check for multiple responses that were made in error**
3. Data should be transcribed from the completed questionnaire to the appropriate web portal**
4. File completed questionnaire in the patient study files**

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

*** Only applicable if a paper PRO questionnaire(s) is utilized as a backup should there be a failure with the electronic device.*

Addressing Problems and Concerns

Occasionally a subject 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 subject that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental, and social health problems of subjects. Emphasize that this information is as important as any of the 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 subject still declines, retrieve the questionnaires. Record the reason for the decline, and thank the subject.

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

In these instances, the coordinator may obtain subject responses by reading out loud each question, followed by the corresponding response categories, and entering the subject's response. No help should be provided to the subject by any person other than the designated study coordinator. The coordinator should not influence subject 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 subject provide responses to the questions. Unless specified in the study protocol proxy data are *not* an acceptable substitute for subject self-report. Subjects 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 subject having trouble understanding particular items, ask the subject 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 subject.

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 subject that his/her answers will be pooled with other subjects' answers and that they will be analyzed as a group rather than as individuals. Tell the subject 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 possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g. noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

While completing the questionnaire, some subjects might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the subject by rereading the question for them *verbatim.* If the subject 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. Subjects 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.

16.6 Appendix 6: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-3 Liver Events 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; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms

TBL: total bilirubin; ULN: upper limit of normal

Table 16-4 Follow up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete appropriate eCRF pages	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete appropriate eCRF pages	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 drug immediately Hospitalize, if clinically appropriate Establish causality Complete appropriate eCRF pages	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 If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete appropriate eCRF pages	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete appropriate eCRF pages	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 appropriate eCRF pages	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 appropriate eCRF pages	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 drug immediately Hospitalize the patient Establish causality Complete appropriate eCRF pages	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 drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete appropriate eCRF pages	Investigator discretion

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms

Criteria	Actions required	Follow-up monitoring

TBL: total bilirubin; ULN: upper limit of normal

[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.